A COMPARATIVE STUDY OF RITUXIMAB AND CYCLOPHOSPHAMIDE AS INDUCTION THERAPY IN ANCA ASSOCIATED VASCULITIS

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BY

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DECLARATION

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ABBREVIATIONS

AAV	ANCA associated vasculitis
AKI	Acute kidney injury
ANA	Anti nuclear antibodies
ANCA	Anti neutrophiliccytoplasmic antibodies
AZA	Azathioprine
C3	Complement 3
C4	Complement 4
CKD	Chronic kidney disease
CYC	Cyclophosphamide
CR	Complete remission
CRP	C – reactive protein
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
GPA	Granulomatosis with polyangiitis
Hb	Hemoglobin
IF	Immunofluorescence
IFTA	Interstitial fibrosis and tubular atrophy
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LM	Light microscopy
MMF	Mycophenolate mofetil
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
PLEX	Plasma exchange
PR	Partial remission
PR3	Proteinase 3
RPGN	Rapidly progressive glomerulonephritis

RPRF	Rapidly progressive renal failure
RTX	Rituximab
SVV	Small vessel vasculitis
TLC	Total leucocyte count
UPCR	Urine protein to creatinine ratio

ABSTRACT

BACKGROUND: ANCA-associated vasculitides affect small-to-medium-size blood vessels, with a predilection for the respiratory tract and kidneys. Renal involvement occurs in 70% of affected patients and is manifested as rapidly progressive glomerulonephritis with pauci-immune necrotizing, crescentic glomerulonephritis on biopsy.

AIM: To assess the comparative efficacy of Rituximab versus Cyclophosphamide in AAV

MATERIALS AND METHODS: This was an open-label, two-group, parallel design, randomized study of 30 patients of ANCA vasculitis comparing a Rituximab based regimen with IV Cyclophosphamide, conducted in Department of Nephrology at DMCH Ludhiana from 1stMarch 2019. All the patients presenting with features of ANCA associated vasculitis with renal involvement from were included in this study.

RESULTS: 30 patients(15 in each group),were followed up for 6 months. Mean age at presentation was 46.4$\pm$5. years in RTX group and 46.7$\pm$5.97 in CYC group with female preponderance. Mean serum creatinine seen in RTX group was slightly higher (4.9 mg/dl) as compared to CYC group(4.5mg/dl). All patients underwent renal biopsy with most common finding pauci immune crescentric glomerulonephritis. Majority of patients having PR3 positivity (86.7%) as compared to MPO (13.3%).11 patients out of 15 (73.3%) in the RTX and 10 patients out of 15 (66.7%) in CYC group reached the primary end point. but the difference was not significant (P = 0.690). There were no significant differences between two groups in the number of total adverse events and serious adverse events.

CONCLUSIONS: In conclusion, this study show that median age of presentation is younger as compared to western population, with c- ANCA (PR3), being most commonly seen in our population. Both Rituximab and Cyclophosphamide can have comparable efficacy as induction agent for AAV.

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INTRODUCTION

Antineutrophil cytoplasm antibody (ANCA)-associated vasculitides are small-vessel vasculitides that include granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg–Strauss syndrome).[1]

ANCA-associated vasculitides affect small-to-medium-size blood vessels, with a predilection for the respiratory tract and kidneys. The incidence is higher in men than in women. The overall annual incidence of vasculitis is 10-20/million with a peak between 65 and 74 years of age.[2]

Constitutional signs and symptoms, such as fever, myalgia, arthralgia, and malaise, often accompany small-vessel vasculitis. Cutaneous lesions, leukocytoclastic angiitis caused by vasculitis or granulomatous lesions, present as palpable purpura and nodules. Central nervous system disease usually results from involvement of the meningeal vessels. Gastrointestinal involvement has been reported in almost one half of the patients with AAV.[3]

The American College of Rheumatology (ACR) in 1990 had proposed classification criteria for seven vasculitis syndromes. This criteria was developed before wide spread ANCA testing, and PAN and MPA were not differentiated.[4]

The European Vasculitis Study Group (EUVAS) criteria for a diagnosis of AAV:

• History of a chronic inflammatory disease

• Exclusion of other causes (such as infection)

• Tissue biopsy showing characteristic histology on biopsy and/or positive ELISA for either PR3 or MPO antibodies with a classical ANCA on immunofluorescence.[5]

The majority of patients with these syndromes have ANCA detectable in the serum at the time of initial presentation.[5] Two types of ANCA are of clinical significance in patients with vasculitis. ANCA causing a cytoplasmic immunofluorescence pattern (C-ANCA) on ethanol-fixed

neutrophils reacting with the neutrophil granule enzyme, proteinase 3 (PR3-ANCA) occur in over 80% of patients with GPA. In contrast, ANCA causing a perinuclear immunofluorescence pattern (P-ANCA) on ethanol-fixed neutrophils and reacting with myeloperoxidase (MPO-ANCA) occur in less than 10% of patients with GPA, but in the majority of patients with MPA.

Using enzyme linked immunoassay (ELISA), C-ANCA commonly has specificity for proteinase 3 (PR3-ANCA) and the most common P-ANCA commonly has specificity for Myeloperoxidase (MPO- ANCA). When used together, positive IFA with positive ELISA has a sensitivity of approximately 81% and a specificity of approximately 96% for pauci-immune crescentic GN.[6]

Renal involvement occurs in 70% of affected patients and is manifested as rapidly progressive glomerulonephritis with pauci-immune necrotizing, crescentic glomerulonephritis on biopsy.[7] Patients with ANCA associated glomerulonephritis usually present with hematuria, proteinuria, and serum creatinine. Use of glucocorticoids and Cyclophosphamide as induction therapy for AAV has improved the survival rates from 20 % to well over 80 % at 2 years.[8]

Despite the improvement in outcomes, not all patients respond satisfactorily to CYC, and up to half of the patients who initially achieve remission relapse within the first 3–5 years.[9] Moreover, substantial toxicity associated with the long-term and repeated use of CYC and GCS has emerged as the principle challenge in the management of these patients. CYC is associated with leukopenia, severe infections, cancer, and ovarian failure.[10] The partial efficacy and severe toxicity of such regimens indicate a need for better induction therapy in ANCA-associated vasculitis.

Rituximab is a B-cell−depleting anti-CD20 monoclonal antibody that has been approved by the European Medicines Agency and the U.S. Food and Drug Administration for the treatment of non-Hodgkin’s lymphoma and rheumatoid arthritis.[11] It can be a treatment option in AAV, offering good response in the form of induction therapy with less propensity for drug toxicity.

AIMS AND OBJECTIVES

- To assess the comparative efficacy of rituximab versus cyclophosphamide in AAV.

REVIEW OF LITERATURE

Vasculitis is characterized by inflammation of blood vessels.[12,13] It constitutes a syndrome encompassing a group of diseases that have a poorly understood etiology abut generally the result of an immunological process that targets the vascular endothelium. The clinical manifestations are highly variable and are related to distal ischemia or bleeding of affected organs or territories.[14]

The extent and severity range from a self-limiting cutaneous condition to potentially fatal multiorgan disease.[15] Vasculitis can be primary or associated with connective tissue, infectious or neoplastic disease.[16]

Inflammation of arteries and veins of the lungs, facial sinuses, and kidneys had been identified as a specific type of chronic granulomatous inflammation. In 1937, Friedrich Wegener, pathologist in Berlin, described that disease which became known as Wegener's granulomatosis. The first case of Wegener"s granulomatosis was described in 1931 by Heinz Klinger in Germany as a variant of PAN and designated "a limited form of periarteritis nodosa''.[17] Although 2 new cases were reported by Hoffman in 1932 and Rossle in 1933, it was pathologist Fredrich Wegener, colleague and friend of Klinger, who, based on 3 cases, established the disease as a defined entity with a characteristic triad [18]: granulomatous inflammation affecting the respiratory tract, granulomatous necrotizing vasculitis, and glomerulonephritis.

In 1951, while at Mount Sinai Hospital in New York, Jacob Churg and Lotte Strauss discovered that disease that carries their name.[19] The disease is characterized by the presence of bronchial asthma, tissue eosinophilia and peripheral eosinophilia, and vasculitis of small and medium vessels, with intravascular and extravascular granulomatous inflammation and with lungs as the main target.[20]

In 1952, Dr. Perla Zeek [21] proposed the first classification of vasculitides and included 5 subgroups that previously described in isolation hypersensitivity angiitis, allergic angiitis, granulomatous angiitis (Churg Strauss), rheumatic arthritis, and temporal arteritis.[22,23]

The best-accepted classification of vasculitides and most used by clinicians and pathologists for decades was proposed by Fauci, that classification evolved from 1978 to 2002. The Fauci classification has important implications for prognosis and treatment since it differentiates between predominantly systemic vasculitis syndromes, hypersensitivity vasculitis, limited in particular to the skin, and polyangiitis overlap syndromes.[24] Surprisingly this changed radically soon after. In 2005 Fauci classified vasculitides as primary and secondary criteria that have been used for decades.

The 1990 American College of Rheumatology classification includes only 7 most common and best characterized vasculitic diseases.[25,26] These criteria identify each vasculitis in an attempt to define the disease.

In 1993, a group of experts met in Chapel Hill in North Carolina, USA, to agree on a classification of vasculitides, define each entity and establish an internationally accepted nomenclature.[27] The system they used for classification was based on the size of the vessels and histopathology findings, to which they added the presence of ANCA. The 1994 International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides (CHCC 1994) proposed names and definitions for the common forms of vasculitis.[4,28,29] The nomenclature was widely adopted. However, in the intervening years, there have been substantial advances in our understanding of vasculitis and a trend to reduce the eponyms in medical terminology. Also, CHCC 1994 focused on a limited number of vasculitides and thus did not propose a nomenclature for some relatively common forms of vasculitis, such as vasculitis secondary to other diseases.[30]

Autoantibodies directed against constituents of polymorphonuclear leukocytes and/or monocytes were first described in 1982 by Davies et al. in a few patients with renal vasculitis.[31] In 1985 it became apparent that ANCA is a sensitive and specific marker for Wegener's granulomatosis.[32] Since then, ANCA has also been described in patients with other forms of vasculitis, i.e. microscopic polyangiitis (Savage et al., 1987)[33], Churg-Strauss syndrome[34], and renal limited

vasculitis (= idiopathic necrotizing crescentic glomerulonephritis.[35] ANCA was originally detected by indirect immunofluorescence on ethanol fixed neutrophils. At least three different patterns of fluorescence have been distinguished: cytoplasmic/classic pattern (cANCA) with accentuation of the fluorescence intensity in the area with the nuclear lobes, a perinuclear pattern (pANCA), and a more diffuse cytoplasmic staining pattern (atypical ANCA).[36] Approximately 90% of the sera that produce a cANCA pattern react with proteinase 3 (PR3), a serine protease from the azurophilic granules of myeloid cells.[37] In patients with primary systemic vasculitis predominantly affecting medium- and small-sized blood vessels, approximately 75% of the sera producing a perinuclear pattern (pANCA) react with myeloperoxidase (MPO), a myeloid lysosomal enzyme. In ANCA-positive patients with other nonvasculitic diseases (e.g. inflammatory bowel disease) often antigenic specificities are recognized, such as lactoferrin and elastase, which may occur.[38] The diagnostic potential of PR3-ANCA and MPO-ANCA are now fairly well established. In a patient with signs and symptoms of vasculitis, ANCA with specificity for PR3 (PR3-ANCA) suggests a diagnosis of Wegener's granulomatosis, whereas ANCA with specificity for MPO (MPO-ANCA) is highly sensitive for either microscopic polyangiitis, idiopathic necrotizing crescentic glomerulonephritis, or active Churg-Strauss syndrome.[39] Several in vitro and animal studies, besides, have suggested that ANCA are involved in the pathophysiology of ANCA related syndromes.

ANCA-associated vasculitis within the spectrum of primary vasculitic syndromes, the ANCA related syndromes form a distinct group with overlapping features. Most patients have a prodromal flu-like onset consisting of malaise, myalgias, arthralgias, fever, and weight loss. This flu-like onset appears within days to weeks before the onset of overt vasculitic or nephritic disease. ANCA associated vasculitis includes four major syndromes: Wegener's granulomatosis, Churg Strauss syndrome, microscopic polyangiitis, and idiopathic necrotizing and/or crescentic glomerulonephritis.[40] Wegener's granulomatosis is

differentiated from the others by the presence of necrotizing granulomatous inflammation of the upper and lower respiratory tract, which is usually accompanied by systemic necrotizing small vessel vasculitis and glomerulonephritis. Churg-Strauss syndrome is differentiated by the presence of (a history of) asthma, allergic rhinitis, systemic eosinophilia, in addition to systemic vasculitis with or without glomerulonephritis.[41] Microscopic polyangiitis is characterized by necrotizing and/or crescentic glomerulonephritis and a multisystem vasculitis involving small vessels. Microscopic polyangiitis shares many features with Wegener's granulomatosis and Churg Strauss syndrome but lacks necrotizing granulomatous inflammation of the respiratory tract and asthma.[3] In idiopathic necrotizing and/or crescentic glomerulonephritis, the vasculitic process is limited to the kidneys. The diseases mentioned above affect people of all ages but are most common in older adults in their 50s and 60s, and they affect men and women equally.[42,43]

Treatment of ANCA vasculitis

For patients with severe systemic AAV, the mainstay of treatment has included high dose glucocorticoids and oral or intravenous cyclophosphamide (CYC).[44] Although effective in 70- 90 % of patients with AAV, the use of CYC, particularly in refractory and relapsing disease is limited owing to cumulative toxicity and serious adverse events.[45] De Groot and colleagues demonstrated that pulse dose of CYC induced remission of AAV as well as daily oral regimens while reducing the cumulative CYC dose by half and significantly decreasing the frequency of treatment-related leucopenia.[46]

Despite the improvement in outcomes, not all patients respond satisfactorily to CYC, and up to half of the patients who initially achieve remission relapse within the first 3-5 years.[47] Moreover, substantial toxicity associated with the long-term and repeated use of CYC and GCS has emerged as the principal challenge in the management of these patients. CYC is associated with leukopenia, severe infections, cancer, and ovarian failure.[48,49]

The partial efficacy and severe toxicity of such regimens indicate a need for better induction therapy in ANCA-associated vasculitis.

In AAV, CYC appears to exert a greater effect on B cells compared to T cells.[50] B cells and their progeny appear to be central in the pathogenesis of AAV through the production of ANCA, as well as T cell co-stimulation and cytokine production.[51] Furthermore, the number of circulating activated B cells correlates with disease activity.[52]

Rituximab is a B-cell−depleting anti-CD20 monoclonal antibody that has been approved by the European Medicines Agency and the U.S. Food and Drug Administration for the treatment of non-Hodgkin's lymphoma and rheumatoid arthritis.[53] Rituximab is a chimeric monoclonal antibody directed against the cell-surface protein CD20, a 297 amino acid phosphoprotein with four transmembrane domains, which is selectively expressed on the cells of B-lymphocyte lineage. The molecule is thought to function as a calcium channel subunit and plays a role in B lymphocyte activation, proliferation, and differentiation.[54] Binding of Rituximab to CD20 causes the death of the target cell by a variety of mechanisms including antibody-dependent cellular cytotoxicity via macrophages and natural killer cells, complement-mediated B cell lysis, apoptosis, and/or sensitization to cytotoxic agents or steroids.[55]

In ANCA-associated vasculitis, B-cell activation and levels of B-cell−activating factor correlate with disease activity.[56] CD20-positive, B-cell−rich, follicle-like areas containing autoreactive memory B cells with an affinity for the ANCA antigen, proteinase 3, are present in Wegener's granulomas.[57] Cyclophosphamide suppresses the activation, proliferation, and differentiation of autoreactive B cells.[58] These findings of a pathogenic role of B cells and ANCAs in ANCA-associated vasculitis provide support for the use of B-cell−targeted therapy. The first use of RTX in AAV was reported in 2001.[59]

A 66-year-old male diagnosed with GPA in 1994 had developed CYC toxicity during subsequent treatment of disease flares, precluding its repeated use. Prednisone in combination with AZA or mycophenolate mofetil (MMF) failed to restore remission during a disease flare. This

prompted the use of RTX on a compassionate-use basis under the hypothesis that remission could be induced by B-lymphocyte depletion resulting in the rapid removal of potentially pathogenic ANCA. The treatment regimen consisted of four weekly RTX doses at 375 mg/m2, accompanied by a prednisone taper. This dosing regimen had been approved by the FDA in 1997 for the use in relapsed or refractory, low grade or follicular B cell non-Hodgkin's lymphoma.[60]

Sustained remissions have been reported in 80 to 90% of patients with refractory ANCA-associated vasculitis who were treated with rituximab.[61] Circulating B lymphocytes remain undetectable in the peripheral blood for about 6–12 months following treatment with Rituximab.[62]

The two randomized trials, RITUXVAS and RAVE, compared the effectiveness of Rituximab compared with Cyclophosphamide as induction treatment in new-onset AAV.

In RITUXVAS trial rituximab-based regimen was not superior to a conventional cyclophosphamide regimen when used as induction treatment in patients with ANCA-associated renal vasculitis, but it permits reduced exposure to CYC and the avoidance of maintenance immunosuppression.[62] In this trial, 44 patients with newly diagnosed GPA or MPA and renal involvement were included. Sustained remissions at 12 months were similar between RTX(76%) and CYC/AZA(82%) groups, demonstrating the efficacy of RTX for remission induction in patients with AAV and significant renal dysfunction. Extended trial follow up data at 24 months show that RTX based induction without maintenance therapy had similar long term outcomes as compared to CYC/AZA regimen about relapse (21% vs 18%) and mortality (18% vs 27%).[63]

In the RAVE trial, IV Rituximab was compared with oral cyclophosphamide. Rituximab and glucocorticoids are not inferior to the standard regimen in patients with severe AAV.[64]

It was a double-blind double-dummy placebo-controlled, non-inferiority trial evaluating a total of 197 patients with GPA or MPA. In contrast to RITUXIVAS, the RAVE trial included both newly diagnosed and

relapsing patients comparing RTX 375 mg/m2 weekly for 4 weeks to 2 mg/kg oral CYC for 3-6 months followed by AZA maintenance. Extended follow up results showed similar long term efficacy between the two regimens with 48% and 39% of patients in sustained remission at 12 months and 18 months in RTX arm and 39% and 33% in sustained remission at 12 months and 18 months in CYC/AZA, respectively

These two trials had some differences. RITUXVAS (*n* = 44) included new patients with severe renal disease whereas RAVE (*n* = 197) included new as well as relapsing patients with well-preserved kidney function. Oral cyclophosphamide was used as a comparator in RAVE, whilst pulsed cyclophosphamide was used in RITUXVAS. In both trials, rituximab was administered as four infusions of 375 mg/m2 body surface area; however, in RITUXVAS, two or three cycles of cyclophosphamide were given in addition to rituximab. Prednisolone was tapered and stopped by 5 months in the RAVE trial whilst it was reduced to 5 mg by 6 months and continued for the rest of the trial in the RITUXVAS trial. Neither trial continued with maintenance immunosuppression in the rituximab group.

Both trials found similar efficacy between Rituximab and Cyclophosphamide-based regimens for patients with a new diagnosis of vasculitis. There were no differences in the time to remission for nephritis or pulmonary manifestations between the Rituximab and Cyclophosphamide groups.

In the MYCYC trial, 140 newly diagnosed patients were randomly assigned to MMF or pulsed cyclophosphamide. All patients received the same oral glucocorticoid regimen and were switched to azathioprine following remission. Non-inferiority was demonstrated for the primary remission endpoint, which occurred in 47 patients (67%) in the MMF group and 43 patients (61%) in the cyclophosphamide group Following remission, more relapses occurred in the MMF group (23 patients, 33%) compared with the cyclophosphamide group (13 patients, 19%).[65]

The trial was a randomized control trial in which 137 patients with ANCA-associated vasculitis and a serum Cr > 5.8mg/dL were randomized to receive either 7 sessions of plasma exchange over a 14 day period or Methyl prednisolone 1000mg iv qd x 3d. In addition to these therapies, all patients also received prednisolone (1mg/kg/day, tapered over 6 months) + CYC (2.5mg/kg/day x 3months) followed by Azathioprine for maintenance of remission.

Importantly, the plasma exchange arm was associated with an improved mortality and improved renal function (43 versus 19% risk of progression to ESRD at one year), and many of the patients in the pheresis arm were actually able to come off dialysis. The benefit was typically seen within the first 3 months of therapy.[66]

However, after median time of almost 4 years, when long-term outcomes of patients with severe AAV that were treated with either PLEX or IV Methylprednisolone as initial adjuvant therapy were assessed , there was no evidence of a net difference between PLEX and IV Methylprednisolone in clinical outcomes.[67]

In the most recent study, PEXIVAS trial, it was seen that among patients with severe ANCA-associated vasculitis, the use of plasma exchange did not reduce the incidence of death or ESKD. A reduced-dose regimen of glucocorticoids was noninferior to a standard-dose regimen with respect to death or ESKD.[68]

MATERIALS AND METHODS

This was an open-label, two-group, parallel design, randomized study of 30 patients of ANCA vasculitis comparing a Rituximab based regimen with IV Cyclophosphamide regimen in the treatment of active 'generalized' AAV. Patient were divided into two treatment groups according to computer generated randomization list. Both groups received IV methylprednisolone, followed by IV Rituximab in one group and IV cyclophosphamide in second group.

Study visits occurred at baseline; at weeks 1, 2, 3, and 4; and monthly thereafter for 6 months. Disease activity was measured on the basis of the BVAS. Written informed consent was taken by all patients

SOURCE OF DATA

This study was conducted in Department of Nephrology at DMCH Ludhiana from 1st march 2019.

All the patients presenting with features of ANCA associated vasculitis with renal involvement from were included in this study

METHOD OF COLLECTION OF DATA

Detailed history of patient was taken, with respect to symptoms of various organ manifestations, duration of symptoms before presentation and complete general physical and systemic examination was done. All patients underwent baseline investigations including hemogram, blood urea, serum creatinine, serum albumin, electrolytes, urine microscopy, dipstick and urinary protein creatinine ratio. Egfr was estimated by CKD EPI equation.

Immunological profile was done including ANCA, (by dot blot strip test and indirect immunofluorescence test/ ELISA), Anti GBM, ANA, Complement levels.

ECG, chest Xray, ultrasound abdomen was done in every patient.

Ultrasound guided renal biopsy was done in all patients, using an automated biopsy gun. The specimen was prepared for light microscopy and immunofluorescence studies. Renal biopsy samples were fixed in 4.5 % buffered formaldehyde for light microscopy. Consecutive serial 3 micrometer specimens were used for histological

staining, including hematoxylin-eosin(H&E), periodic acid Schiff (PAS), Jones Silver Methanamine and Masson's trichrome(MT).

Treatment regimes

Dose of Glucocorticoids

All patients in both groups received methylprednisolone pulse (1g IV), followed by prednisolone 1mg/kg/day. After the first 2–4 weeks of treatment, the dose of glucocorticoids was reduced by approximately 10% every 1 to 2 weeks to achieve a half-dose (0.5 mg/kg/d) at approximately the third month of treatment.

Dose of rituximab

For induction therapy, patients in RTX group received premedication with 1g paracetamol and chlorpheniramine 10 mg IV followed by 4 doses of 350 mg/m2 of IV Rituximab once weekly for 4 weeks.

Dose of cyclophosphamide

Patients in CYC group received 3-6 doses of CYC 15 mg/kg, first 3 doses given at 2 weeks interval, following doses given every 3 weekly. Dose reduction according to creatinine > 3 mg/dl was done (12.5 - 10 mg/kg/puls), minimum for 3 months was given in 12 patients. CYC was switched to AZA (2mg/kg/day) after 3 months in those patients who achieved remission

Additional treatment

All patients received calcium and vitamin D supplementation, Proton pump inhibitor, PCP prophylaxis (Cotrimoxazole + Sulfamethoxazole)

INCLUSION CRITERIA

1. A new diagnosis of WG, MP or renal-limited vasculitis (RLV)
2. Renal involvement attributable to active WG, MP or RLV with at least one of the following:
   a) Biopsy demonstrating necrotizing glomerulonephritis.
   b) Red cell casts on urine microscopy or ≥ ++ haematuria
3. ANCA positivity ANCA positivity requires either (a) or (b)
   (a) PR3-ANCA by ELISA.
   (b) MPO-ANCA by ELISA.
4. Written informed consent

EXCLUSION CRITERIA

1. Previous cyclophosphamide, (greater than 2 weeks of an oral or IV pulse cyclophosphamide regimen).
2. Co-existence of another multisystem autoimmune disease, e.g. SLE, Henoch Schonlein Purpura, rheumatoid vasculitis, essential mixed cryoglobulinaemia.
3. Hepatitis B antigen positive or Hepatitis C antibody positive.
4. Pregnancy, breast feeding or inadequate contraception if female.
5. Allergy to a study medication
6. Live Vaccine within last 4 weeks.
7. Known HIV positive (HIV testing will not be a requirement for this trial).
8. Sepsis/ uncontrolled infections
9. Uncontrolled diabetes
10. Treatment Failures Caused by Uncontrolled Disease after 3 months of therapy will be excluded from study.

RANDOMISATION

Patients were randomly assigned, in a 1:1 ratio, to investigational therapy (the rituximab group) or standard therapy (the control group), according to computer generated randomization list.

END POINTS

PRIMARY

1. Induction of complete/ partial remission by 6 months.
2. Treatment Failures Caused by Uncontrolled Disease(3 months)

SECONDARY

Efficacy

1. Response rate at 6 weeks (BVAS < 50% baseline)
2. Remission at 6 months (BVAS=0 for 2 months by 6 months)
3. Time to remission (BVAS=0)
5. Change in eGFR

Remission definition

Full clinical remission is indicated by complete absence of clinical disease activity using BVAS 2003: BVAS score 0 for 2 months. The absence of renal disease activity is indicated by stable or falling

creatinine and the absence of red cell casts. Diagnosis of complete remission is supported by a normal C-reactive protein. Sustained remission is defined by BVAS 0, maintained for at least 6 months

Partial remission (PR) was defined as clinically relevant improvement of disease activity without fulfilling the criteria for CR

Escape treatment

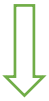
Failure to recover renal function:

Patients with renal-limited disease who remained dialysis-dependent, were planned for withdrawal of immunosuppressive therapy after three months (treatment failure).These 2 patients expired in both groups. No patients required switch over therapy. No patients were withdrawn from study.

STUDY DESIGN

ENTRY

INCLUSION CRITERIA



RANDOMISATION

(1:1)

RITUXIMAB	CYCLOPHOSPHAMIDE
15 patients	15 patients
375 mg/m^2 IV 4 doses	(3 – 6 months)
Methyl prednisolone 1g IV	Methyl prednisolone 1gIV
Prednisolone 1mg/kg/d	Prednisolone 1mg/kg/d

6 MONTHS

1 death	1 death
10 patients : CR	10 patients: CR
1 patient : PR	0 patients : PR

6 WEEKS: INITIAL ASSESSMENT

6 MONTHS: EFFICACY AND SAFETY

OBSERVATIONS AND RESULTS

This was an open-label, two-group, parallel design, randomized study of 30 patients of ANCA vasculitis comparing a Rituximab based regimen with IV Cyclophosphamide, conducted in Department of Nephrology at DMCH Ludhiana from 1st March 2019. All the patients presenting with features of ANCA associated vasculitis with renal involvement were included in this study**.**

I BASELINE CHARACTERISTICS OF PATIENTS

TABLE 1: AGE DISTRIBUTION OF PATIENTS

In baseline characteristics, mean age was 46.4±5. years in RTX group and 46.7 ±5.97 in CYC group.

	RTX		CYC		T	p-value	**Difference**		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
Age	46.47	5.04	46.73	5.97	-0.132	0.896	-0.27	2.02	-4.40	3.87

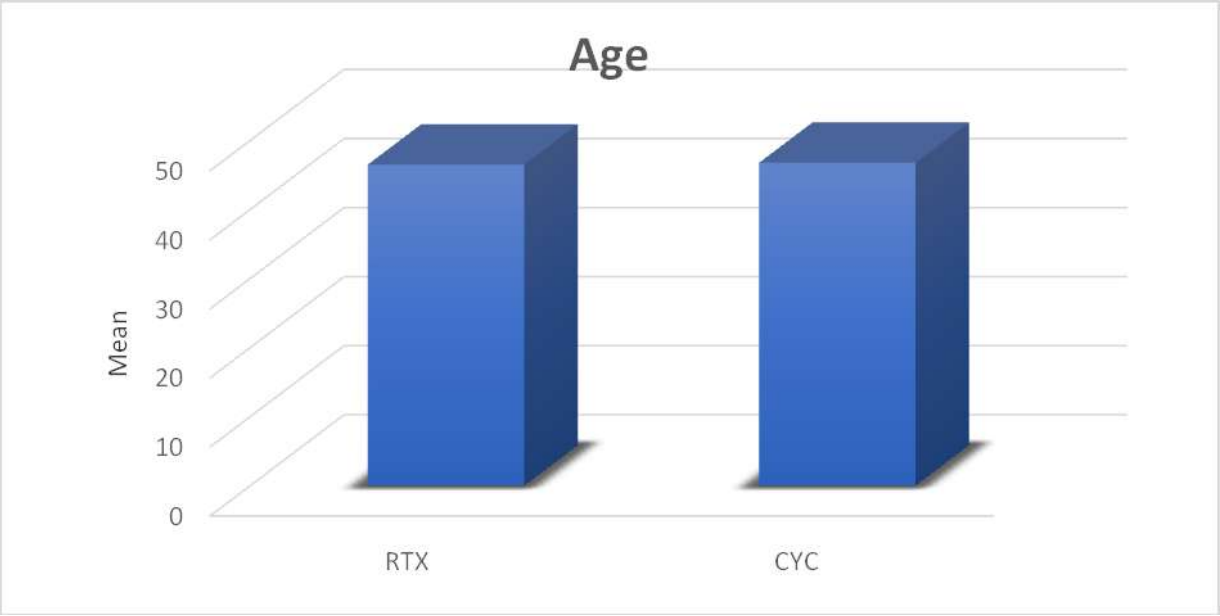


FIG 1: AGE DISTRIBUTION OF PATIENTS

TABLE 2: SEX DISTRIBUTION OF PATIENTS

		Group				Total	Chi-square value	p-value
		RTX		CYC				
SEX	F	9	60.0%	10	66.7%	19	0.144	0.705
	M	6	40.0%	5	33.3%	11		

Female preponderance was seen in both groups 9 (60%) in RTX and 10 (66.7%) IN CYC group.

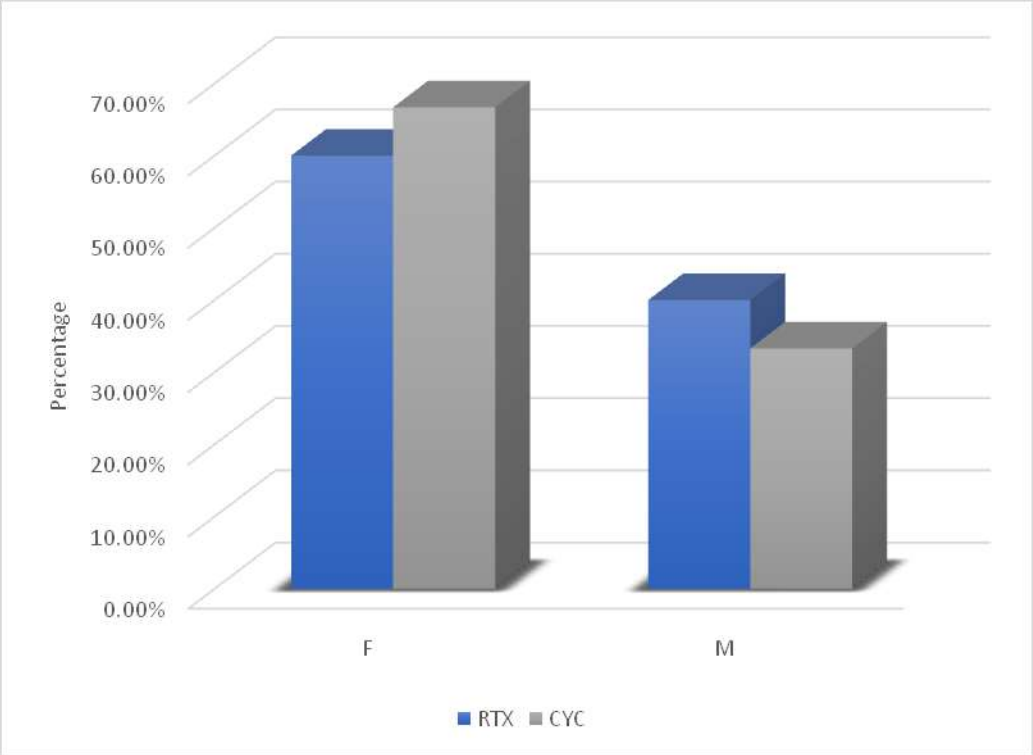


FIG 2: SEX DISTRIBUTION OF PATIENTS

TABLE 3: CONSTITUTIONAL SYMPTOMS AT BASELINE

		Group				Total	Chi-square value	p-value
		RTX		CYC				
WEIGHT LOSS	N	6	40.0%	7	46.7%	13	0.136	0.713
	Y	9	60.0%	8	53.3%	17		
ARTHRALGIA	N	9	60.0%	9	60.0%	18	0.000	1.000
	Y	6	40.0%	6	40.0%	12		
FEVER	N	4	26.7%	6	40.0%	10	0.600	0.439
	Y	11	73.3%	9	60.0%	20		
MYALGIA	N	10	66.7%	9	60.0%	19	0.144	0.705
	Y	5	33.3%	6	40.0%	11		

Most common symptoms at presentation were constitutional symptoms including fever: 73.3% in RTX, 60% in CYC group), arthalgias: 40 % both in RTX and CYC group. myalgias (33.3% in RTX and 40% in CYC group), weight loss (60% in RTX and 53.3% in CYC group).

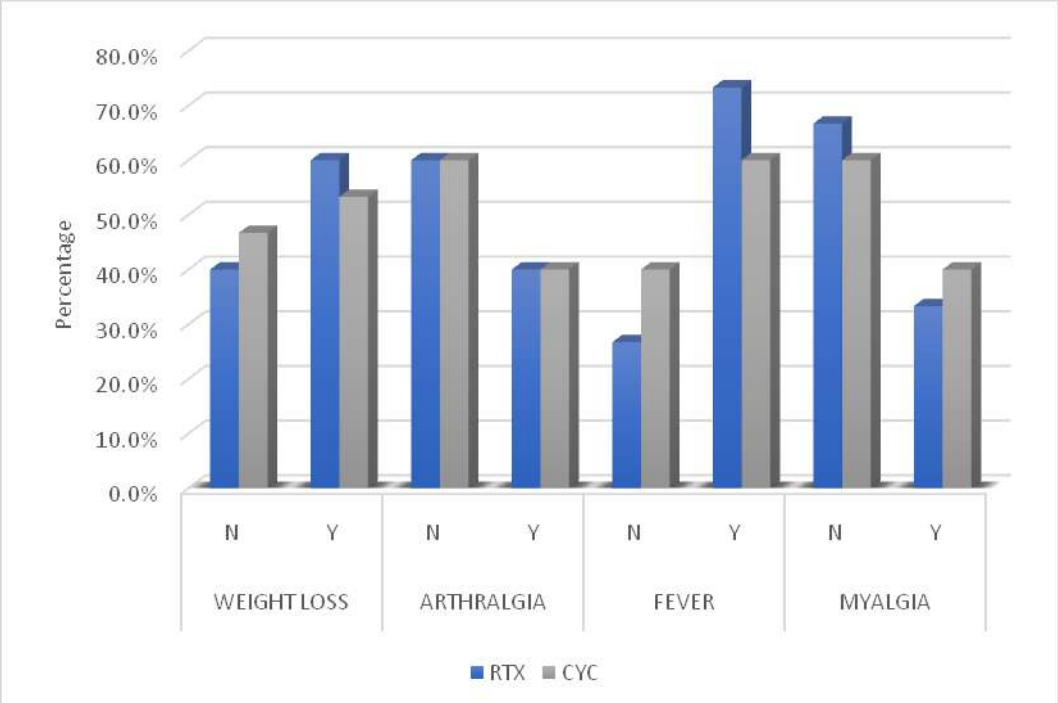


FIG 3: CONSTITUTIONAL SYMPTOMS AT BASELINE

TABLE 4: CUTANEOUS INVOLVEMENT AT BASELINE

		Group				Total	Chi-square value	p-value
		RTX		CYC				
INFARCT	N	15	100.0%	15	100.0%	30		
PURPURA	N	12	80.0%	13	86.7%	25	0.240	0.624
	Y	3	20.0%	2	13.3%	5		
ULCER	N	13	86.7%	13	86.7%	26	0.000	1.000
	Y	2	13.3%	2	13.3%	4		
GANGRENE	N	15	100.0%	15	100.0%	30		
OTHER	N	15	100.0%	15	100.0%	30		

Skin involvement was in form of purpura, ulcers and gangrene. purpura was seen in 20% patients in RTX and 13% patients in CYC group. Ulcers were present in 13.3 % patients in both groups.

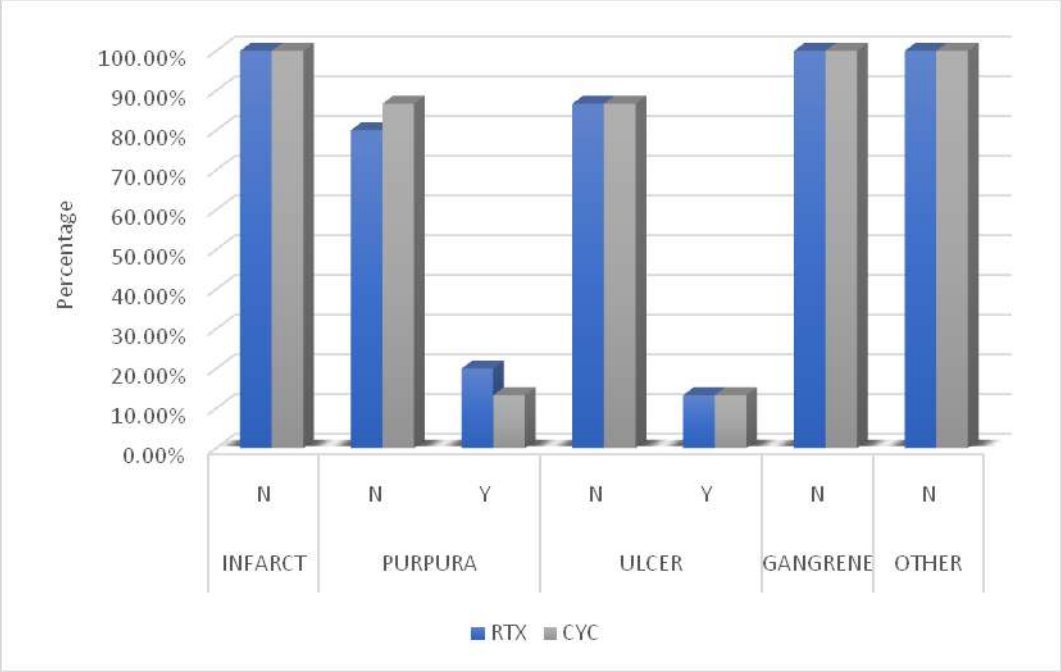


FIG 4: CUTANEOUS INVOLVEMENT AT BASELINE

TABLE 5: ENT INVOLVEMENT AT BASELINE

		Group				Total	Chi-square value	p-value
		RTX		CYC				
BLOODY NASAL DISCHARGE/ CRUSTING/ ULCERS	N	10	66.7%	11	73.3%	21	0.159	0.690
	Y	5	33.3%	4	26.7%	9		
SINUS INVOLVEMENT	N	9	60.0%	10	66.7%	19	0.144	0.705
	Y	6	40.0%	5	33.3%	11		
SWOLLEN SALIVARY GLANDS	N	15	100.0%	15	100.0%	30		
SUBGLOTTIC INFL.	N	14	93.3%	15	100.0%	29	1.034	0.309
	Y	1	6.7%	0	0.0%	1		
CONDUCTIVE DEAFNESS	N	14	93.3%	14	93.3%	28	0.000	1.000
	Y	1	6.7%	1	6.7%	2		
SENSORINEURAL DEAFNESS	N	13	86.7%	13	86.7%	26	0.000	1.000
	Y	2	13.3%	2	13.3%	4		

Upper respiratory tract was involved in (60% patients in RTX group and 66.7 % in CYC group). Majority of patients had paranasal sinus involvement (60% in RTX group and 66.7% in CYC group.1 patient (6.7%) in RTX group had subglottic inflammation. 1 patient had conductive deafness in each group (6.7%). 2 patients had sensorineural deafness in each group (13.3%)

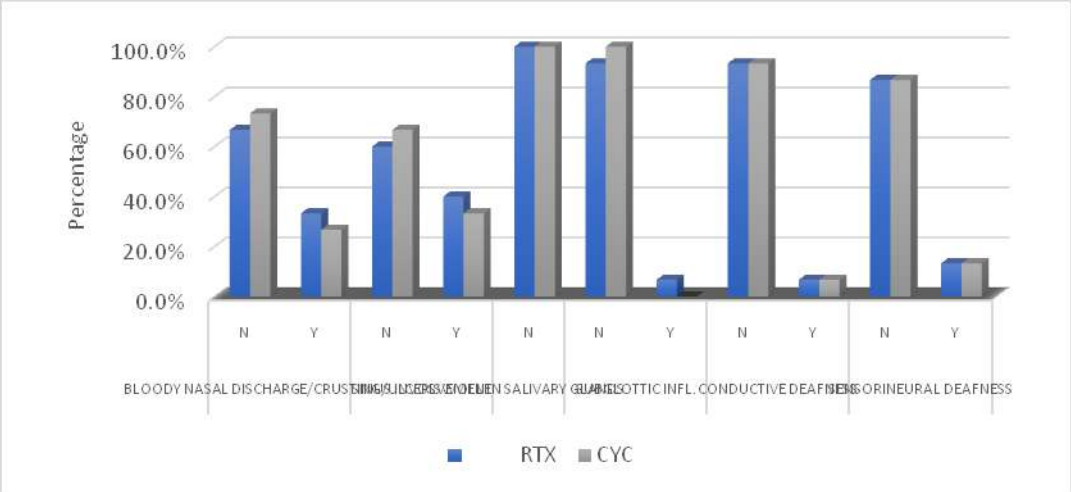


FIG 5: ENT INVOLVEMENT AT BASELINE

TABLE 6: PULMONARY SYSTEM INVOLVEMENT AT BASELINE

		Group				Total	Chi-square value	p-value
		RTX		CYC				
PLEURISY	N	13	86.7%	13	86.7%	26	0.000	1.000
	Y	2	13.3%	2	13.3%	4		
NODULES/ CAVITY	N	13	86.7%	13	86.7%	26	0.000	1.000
	Y	2	13.3%	2	13.3%	4		
INFILTRATES	N	9	60.0%	8	53.3%	17	0.136	0.713
	Y	6	40.0%	7	46.7%	13		
ENDOBRONCHIAL INVOLVEMENT	N	15	100.0%	15	100.0%	30		
HAEMOPTYSIS/ ALVEOLAR HEMORRHAGE	N	11	73.3%	12	80.0%	23	0.186	0.666
	Y	4	26.7%	3	20.0%	7		
RESPIRATORY FAILURE	N	13	86.7%	13	86.7%	26	0.000	1.000
	Y	2	13.3%	2	13.3%	4		

40 % patients in RTX group and (46.7%) in CYC group had pulmonary involvement in the form of cavities (13.3% in each group), infiltrates(40 % in RTX , 46.7 % in CYC group) and DAH (26.7% in RTX and 20% in CYC group).13.3% of patients had respiratory failure in each group.

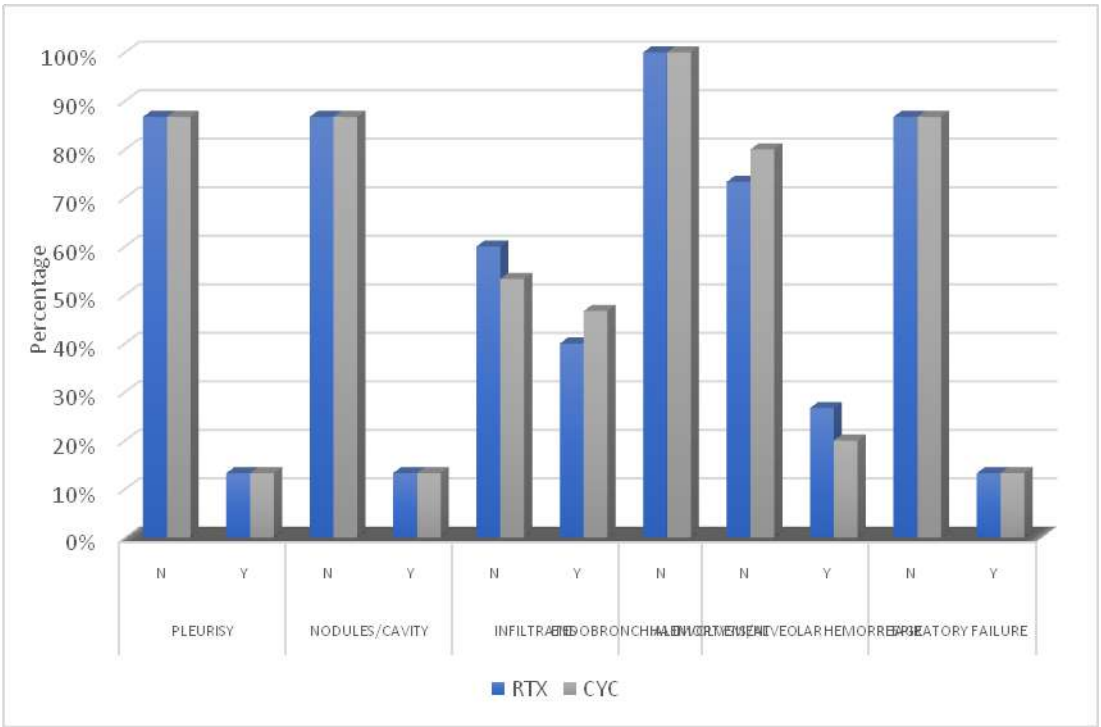


FIG 6: PULMONARY SYSTEM INVOLVEMENT AT BASELINE

TABLE 7: NERVOUS SYSTEMINVOLVEMENT AT BASELINE

		Group				Total	Chi-square value	p-value
		RTX		CYC				
MENINGITIS	N	15	100.0%	15	100.0%	30		
CORD LESION	N	15	100.0%	15	100.0%	30		
STROKE	N	15	100.0%	15	100.0%	30		
CRANIAL NERVE PALSY	N	15	100.0%	15	100.0%	30		
SPN	N	15	100.0%	14	93.3%	29	1.034	0.309
	Y	0	0.0%	1	6.7%	1		
M.M.M	N	14	93.3%	15	100.0%	29	1.034	0.309
	Y	1	6.7%	0	0.0%	1		

Nervous system involvement in the form of peripheral neuropathy was seen in 1 patient (6.7%) of patients in CYC group. Mononeuritis multiplex was seen in 1 patient(6.7% in RTX group.

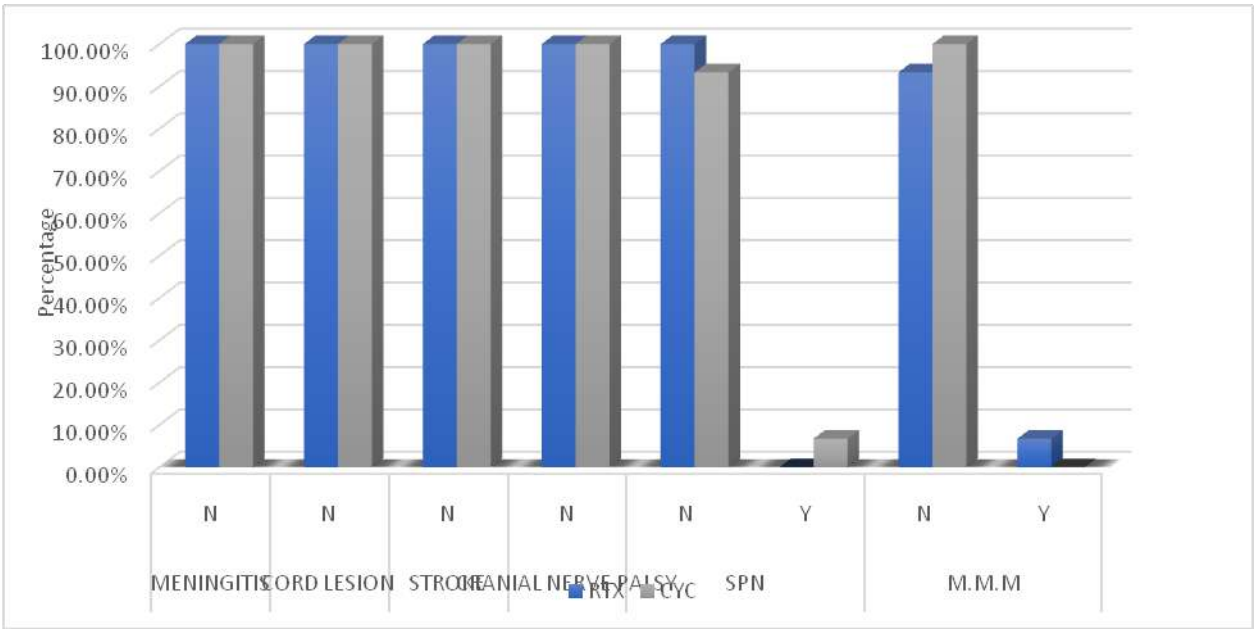


FIG 7: NERVOUS SYSTEM INVOLVEMENT AT BASELINE

TABLE 8: RENALSYMPTOMS AT PRESENTATION

		Group				Total	Chi-square value	p-value
		RTX		CYC				
PEDAL EDEMA	N	8	53.3%	10	66.7%	18	0.556	0.456
	Y	7	46.7%	5	33.3%	12		
OLIGURIA	N	11	73.3%	11	73.3%	22	0.000	1.000
	Y	4	26.7%	4	26.7%	8		
HYPERTENSION	Y	15	100.0%	15	100.0%	30		
PROTEINURIA	Y	15	100.0%	15	100.0%	30		
GROSS HAEMATURIA	N	13	86.7%	12	80.0%	25	0.240	0.624
	Y	2	13.3%	3	20.0%	5		

Renal symptoms were macroscopic hematuria seen in 13.3% of patients in RTX group and 20 % patients in CYC group, hypertension seen in 100% patients in both groups)

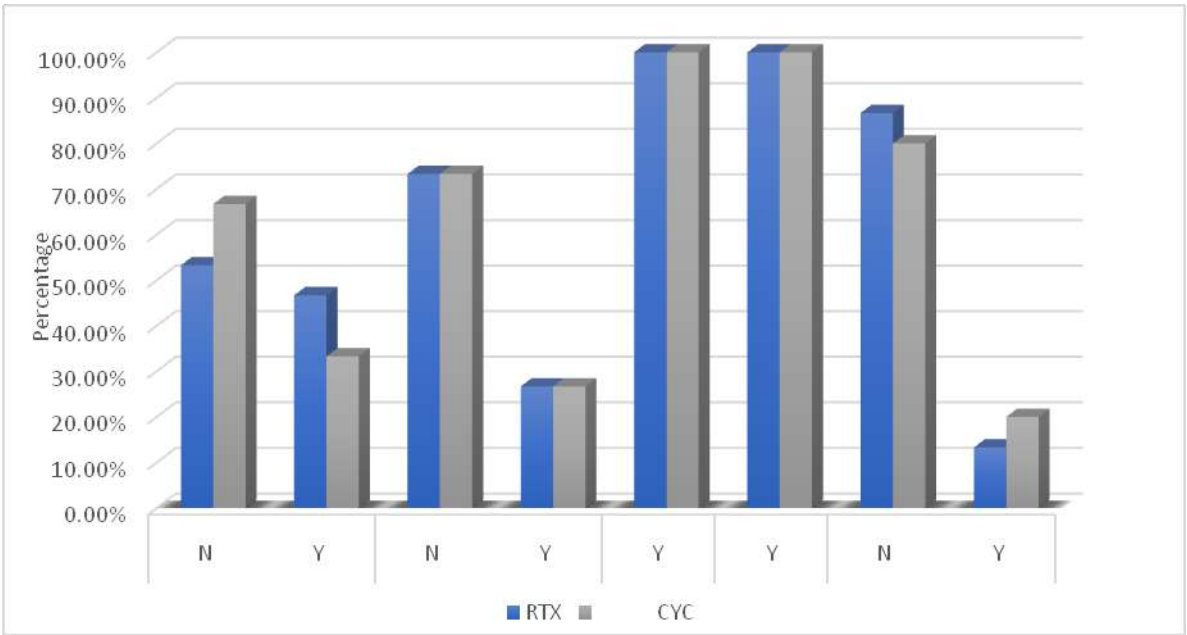


FIG 8: RENAL SYMPTOMS AT PRESENTATION

TABLE 9: RENAL INVESTIGATIONS AT BASELINE

	RTX		CYC		t	p-value	**Difference**		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
CREAT BASELINE	4.94	2.05	4.57	1.87	0.511	0.613	0.37	0.72	-1.10	1.84
EGFR BASELINE	14.80	7.50	15.60	10.32	-0.243	0.810	-0.80	3.30	-7.55	5.95
RBC BASELINE	20.47	5.89	18.80	5.56	0.797	0.432	1.67	2.09	-2.62	5.95
UPCR BASELINE	2.70	0.56	2.29	0.47	2.148	0.041	0.41	0.19	0.02	0.79

Mean serum creatinine seen in RTX group was 4.9 mg/dl(mean e GFR 14.8 ml/min/1.73 m^2) as compared to 4.57 mg/dl in CYC group with mean e GFR OF 15.6 ml/min/1.73 m2. All patients underwent renal biopsy with most common finding pauci immune crescentric glomerulonephritis.

Urinary findings at baseline were microscopic hematuria and proteinuria (100% patients in both groups).

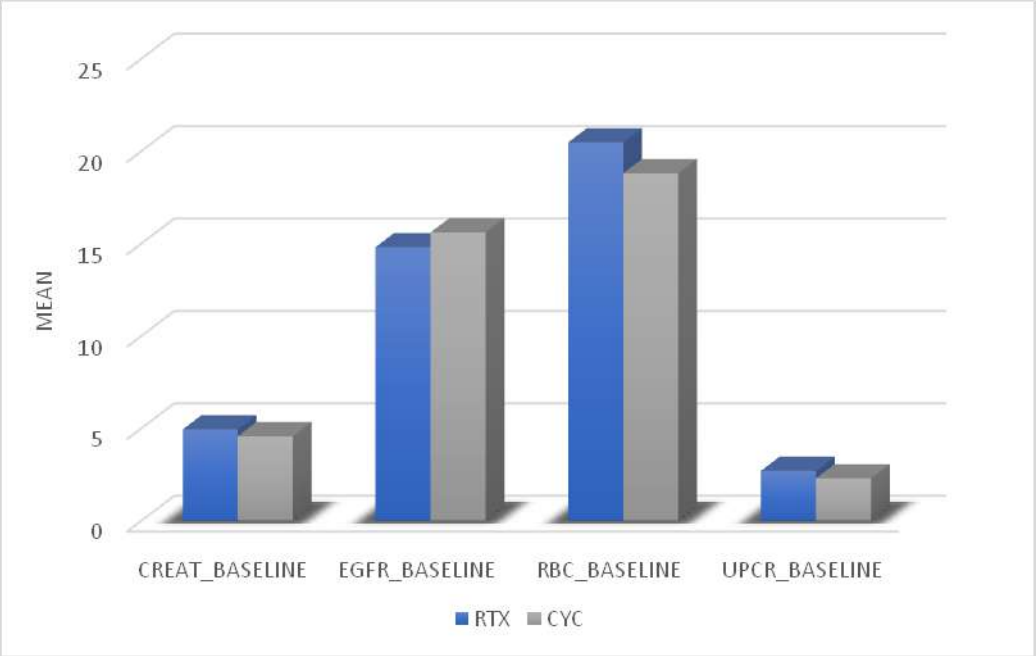


FIG 9: RENAL INVESTIGATIONS AT BASELINE

TABLE 10: TYPE OF AAV

		Group				Total	Chi-square value	p-value
		RTX		CYC				
ANCA TYPE	MPO	2	13.3%	2	13.3%	4	0.000	1.000
	PR3	13	86.7%	13	86.7%	26		
ANCA Baseline	+	15	100.0%	15	100.0%	30		

86.7 % patients had GPA in both groups. Only minority of patients had MPA (13.3% in both groups).

All patients had ANCA positivity by immunoblot assay. Majority of patients having PR3 positivity(86.7%) as compared to MPO(13.3%).

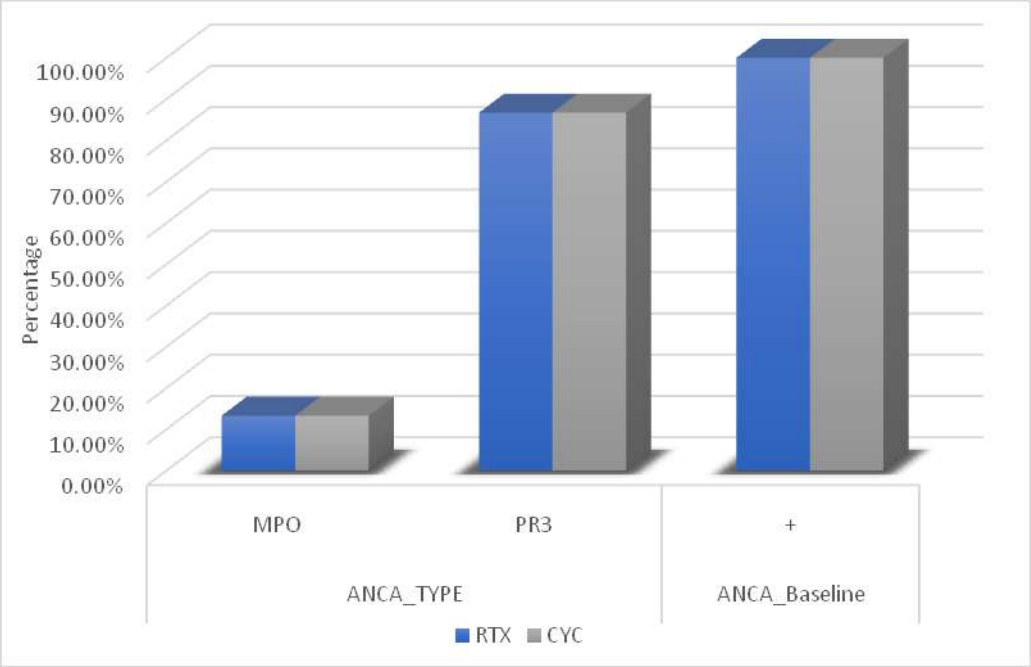


FIG 10: TYPE OF AAV

TABLE 11: BVAS SCORE AT BASELINE

	RTX		CYC		t	p-value	**Difference**		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
BVAS BASELINE	20.13	2.97	20.00	3.57	0.111	0.912	0.13	1.20	-2.32	2.59

Mean BVAS score was 20.13 in RTX group and 20 in CYC group at presentation.

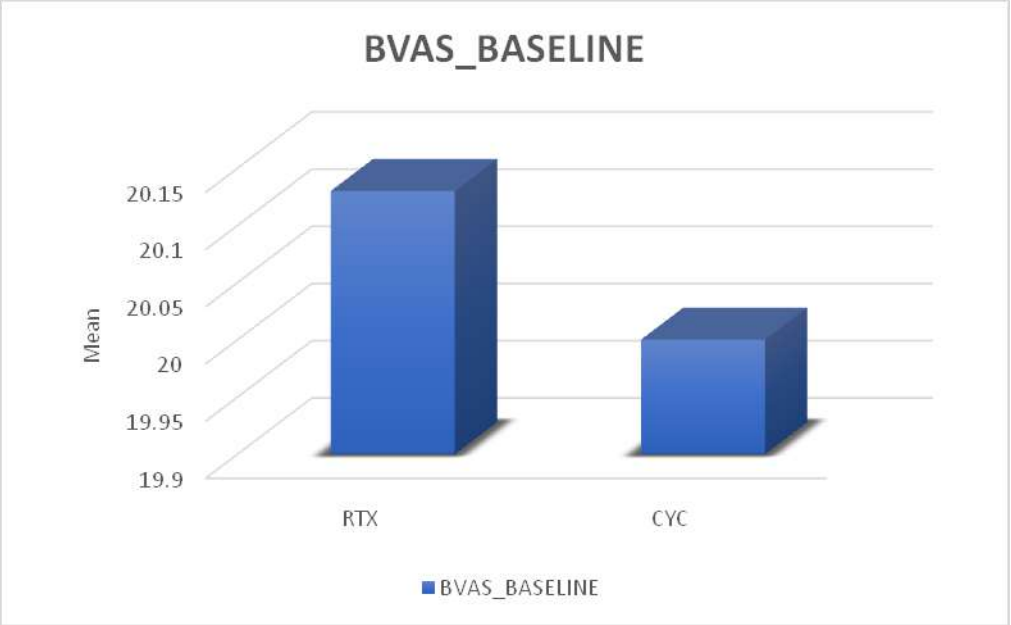


FIG 11: BVAS SCORE

TABLE 12. TYPE OF ANCA AND NEED FOR HD/PLEX

		Group				Total	Chi-square value	p-value
		RTX		CYC				
AAV	GPA	13	86.70%	13	86.70%	26	0	1
	MPA	2	13.30%	2	13.30%	4		
PLEX	N	13	86.70%	13	86.70%	26	0	1
	Y	2	13.30%	2	13.30%	4		
HD	N	13	86.70%	13	86.70%	26	0	1
	Y	2	13.30%	2	13.30%	4		

86.7 % patients had GPA in both groups. Only minority of patients had MPA (13.3% in both groups). 13.3 % of patients required HD and PLEX in both groups.

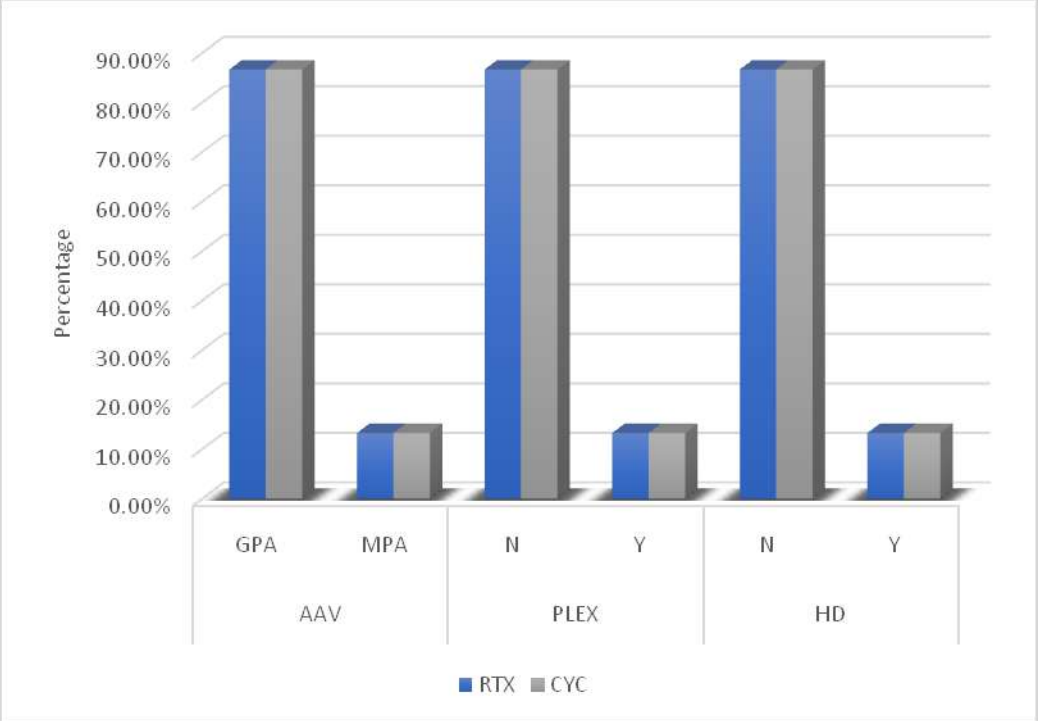


FIG 12: TYPE OF ANCA

II. TREATMENT REGIMES

TABLE 13: DOSE OF PREDNISOLONE

	RTX		CYC		t	p-value	**Difference**		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
PREDNISOLONE DOSE_BASELINE	60.00	.000[b]	60.00	.000[b]						
PREDNISOLONE DOSE_3RD MONTH	13.93	2.72	13.93	2.72	0.000	1.000	0.00	1.03	-2.12	2.12
PREDNISOLONE DOSE_6TH MONTH	5.71	1.82	5.71	1.82	0.000	1.000	0.00	0.69	-1.41	1.41

All patients in both groups received methylprednisolone pulse (1g IV), followed by prednisolone 1mg/kg/day. Dose was tapered to 15 mg/day at 8 weeks in both groups. It was further tapered to 5 mg/day at the end of 6 months in 10 patients in both groups.

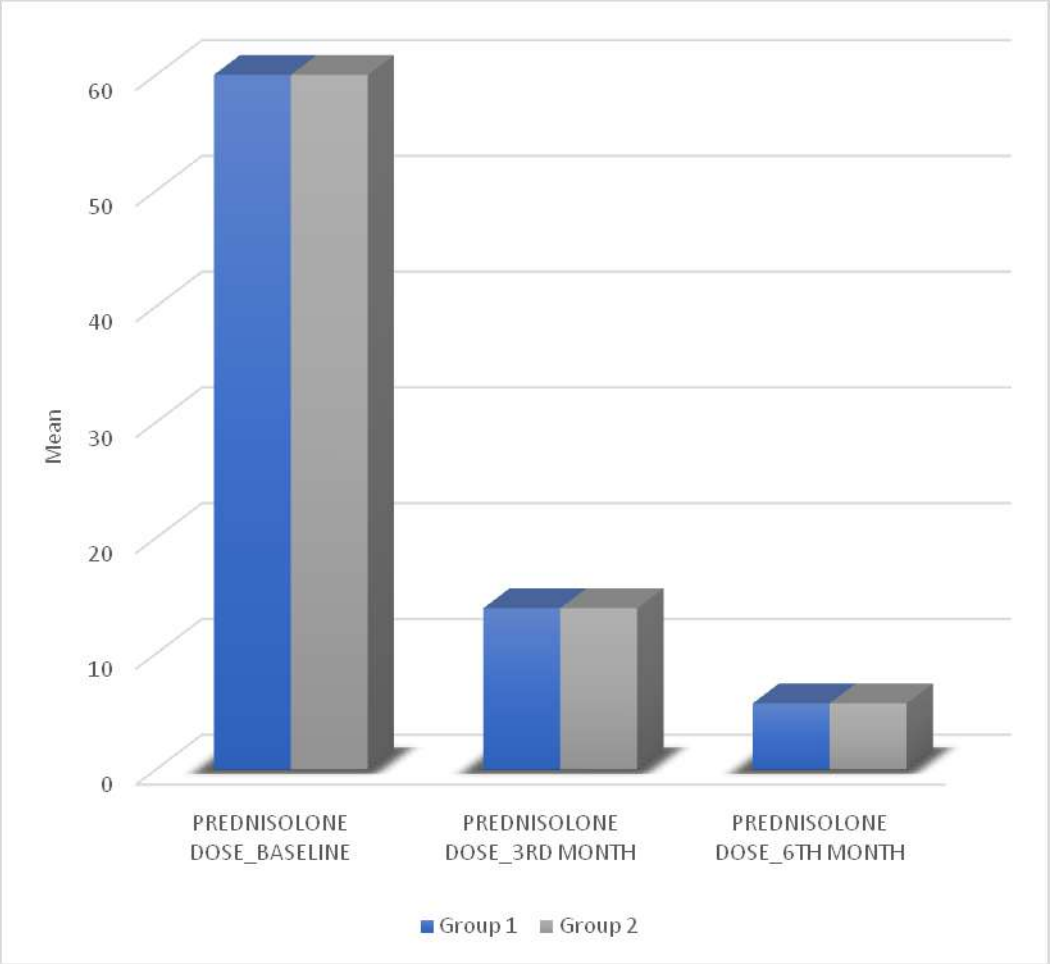


FIG13: DOSE OF PREDNISOLONE

III EFFICACY ASSESSMENT

- PRIMARY END POINTS:
  1. Induction of complete/ partial remission by 6 months.
  2. Treatment Failures Caused by Uncontrolled Disease (3 months)

1. INDUCTION OF PARTIAL/COMPLETE REMISSION BY MONTHS

TABLE 14: COMPARISION OF COMPONENTS OF REMISSION

	RTX		CYC		t	p-value	**Difference**		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
CREAT_BASELINE	4.94	2.05	4.57	1.87	0.511	0.613	0.37	0.72	-1.10	1.84
Sixth Month	1.52	1.09	1.71	1.43	-0.387	0.702	-0.19	0.48	-1.17	0.80
Baseline-6 month	3.19	1.17	2.61	1.37	1.202	0.240	0.58	0.48	-0.41	1.57
EGFR_BASELINE	14.80	7.50	15.60	10.32	-0.243	0.810	-0.80	3.30	-7.55	5.95
Sixth Month	73.29	38.55	66.86	37.69	0.446	0.659	6.43	14.41	-23.19	36.04
Baseline-6 month	-57.86	32.54	-50.50	31.69	-0.606	0.550	-7.36	12.14	-32.31	17.59
BVAS_BASELINE	20.13	2.97	20.00	3.57	0.111	0.912	0.13	1.20	-2.32	2.59

Sixth Month	2.14	3.63	2.14	3.63	0.000	1.000	0.00	1.37	-2.82	2.82
Baseline-6 month	17.71	2.13	17.29	2.52	0.486	0.631	0.43	0.88	-1.39	2.24
CRP_BASELINE	58.40	25.19	53.87	24.76	0.497	0.623	4.53	9.12	-14.15	23.21
Sixth Month	7.21	6.03	7.29	5.81	-0.032	0.975	-0.07	2.24	-4.67	4.53
Baseline-6 month	-47.36	17.70	-43.29	18.72	0.591	0.559	4.07	6.88	-10.08	18.22
RBC_BASELINE	20.47	5.89	18.80	5.56	0.797	0.432	1.67	2.09	-2.62	5.95
Sixth Month	1.86	3.72	3.07	4.45	-0.784	0.440	-1.21	1.55	-4.40	1.97
Baseline-6 month	18.29	6.63	15.29	5.00	1.352	0.188	3.00	2.22	-1.56	7.56
UPCR_BASELINE	2.70	0.56	2.29	0.47	2.148	0.041	0.41	0.19	0.02	0.79
Sixth Month	0.54	0.74	0.47	0.59	0.275	0.786	0.07	0.25	-0.45	0.59
Baseline-6 month	2.21	0.87	1.84	0.89	1.099	0.282	0.37	0.33	-0.32	1.05

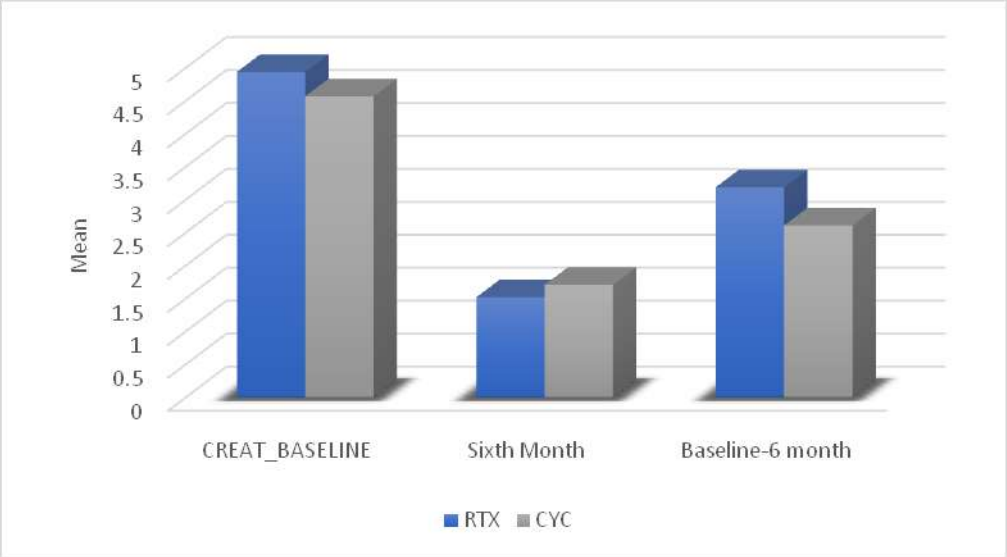


FIG 14.1: CREATININE: BASELINE TO 6 MONTHS

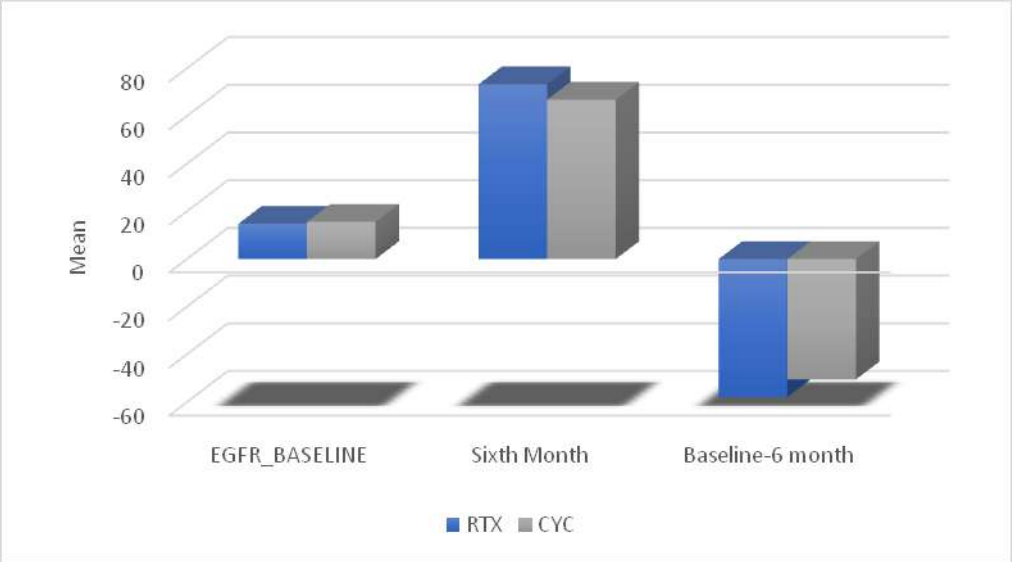


FIG 14.2: ESTIMATED GFR: BASELINE TO 6 MONTHS

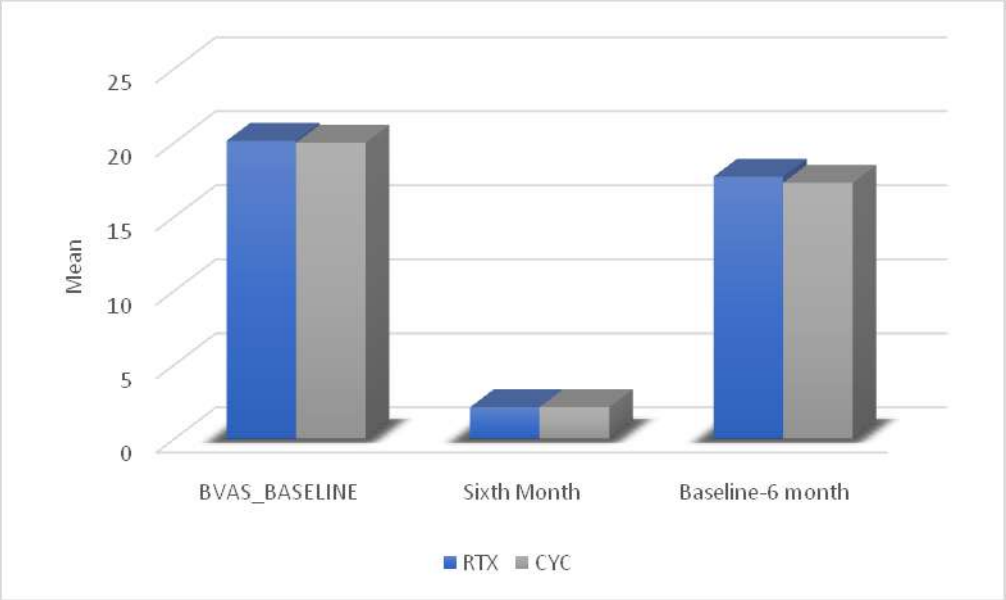


FIG 14.3: BVAS: BASELINE TO 6 MONTHS

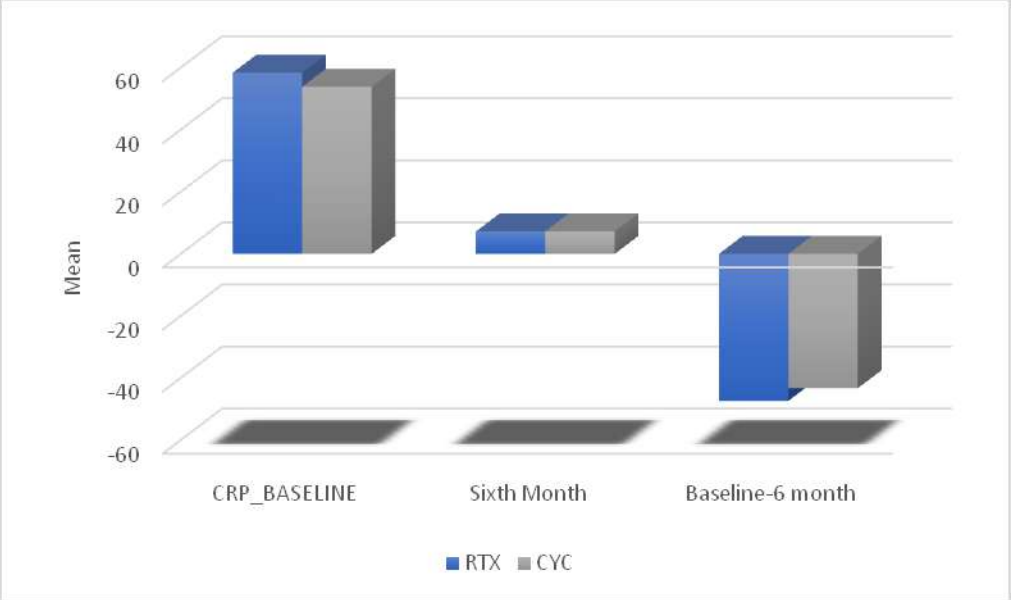


FIG 14.4: CRP: BASELINE TO 6 MONTHS

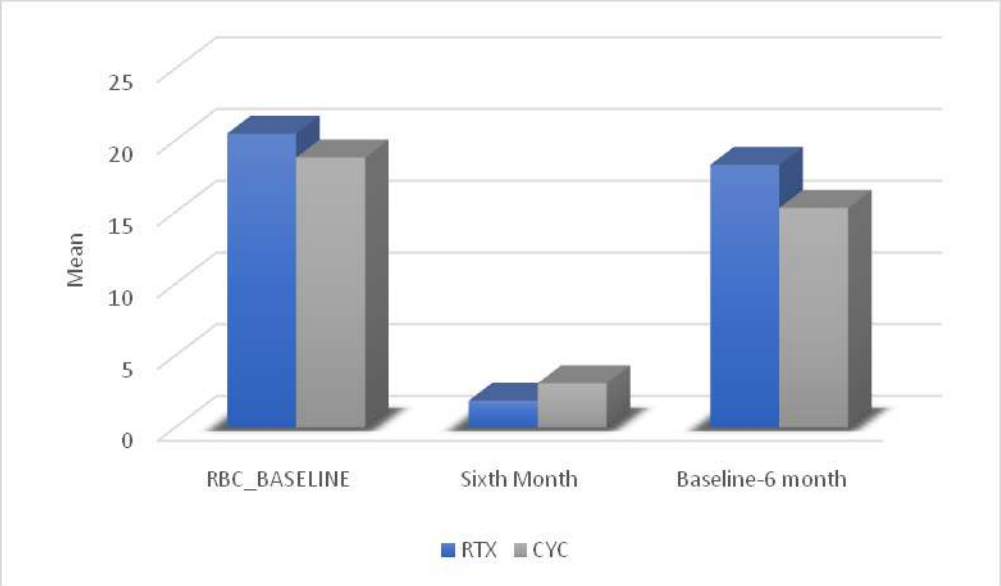


FIG 14.5: URINE RBCs: BASELINE TO 6 MONTHS

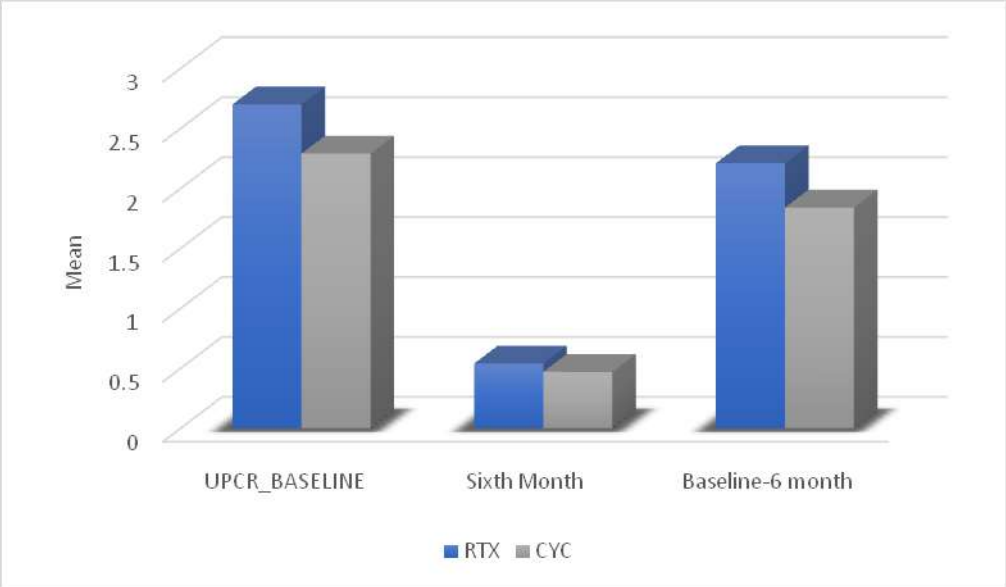


FIG 14.6: UPCR: BASELINE TO 6 MONTHS

2. OUTCOME

TABLE 15: OUTCOME OF PATIENTS AT 6 MONTHS

		Group				Total	Chi-square value	p-value
		RTX		CYC				
REMISSION	N	4	26.7%	5	33.3%	9	0.159	0.690
	Y	11	73.3%	10	66.7%	21		
OUTCOME	DEATH	1	6.7%	1	6.7%	2	1.143	0.767
	NO REMISSION	3	20.0%	4	26.7%	7		
	PARTIAL REMISSION	1	6.7%	0	0.0%	1		
	REMISSION	10	66.7%	10	66.7%	20		

11patients out of 15 (73.3%) in the RTX and 10 patients out of 15 (66.7%) in CYC group reached the primary end point. The proportion of patients who reached the primary end point was more in the rituximab group than in the CYC group, but the difference was not significant (P = 0.690). 11patients treated with rituximab (73%) reached the secondary endpoint of disease remission while receiving less than 10 mg per day of prednisone, as compared with 10 patients in CYC group (63%,P = 0.10).

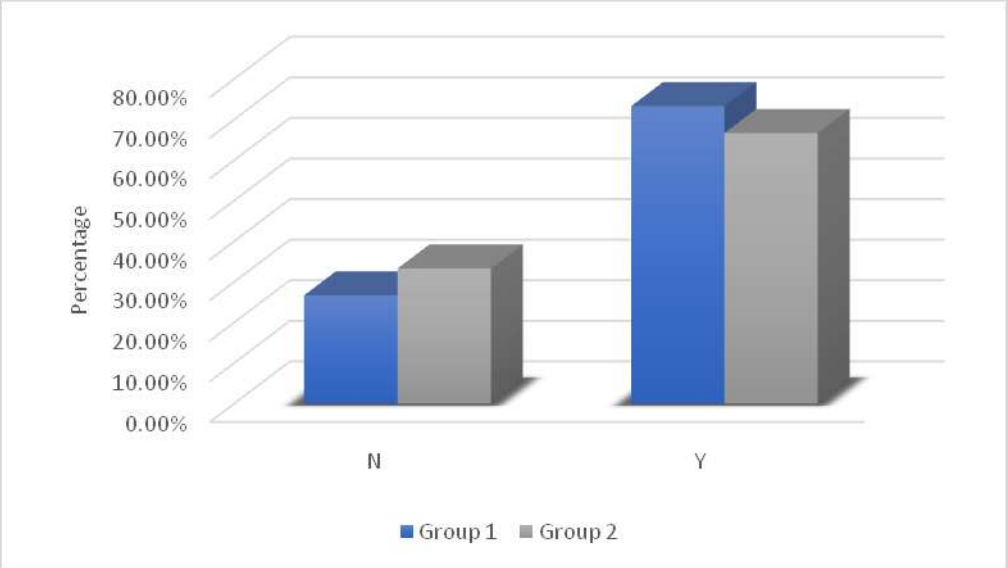


FIG 15.1: COMPARISION OF REMISSION AT 6 MONTHS

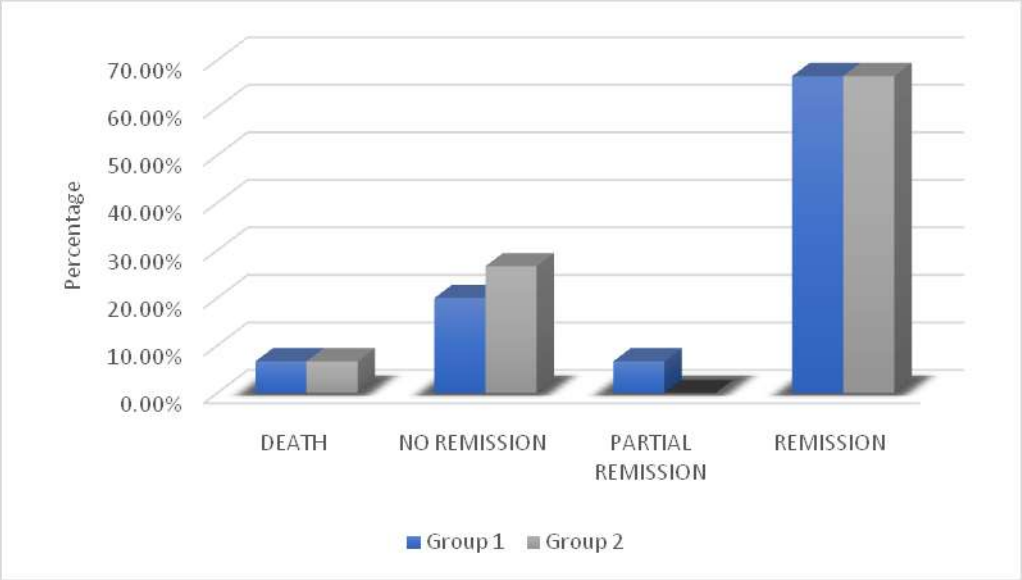


FIG 15.2: OUTCOMES AT 6 MONTHS

TABLE 16: OUTCOME: COMPARISION OF NUMBER OF DEATHS

		Group				Total	Chi-square value	p-value
			Group 1		Group 2			
OUTCOME	DEATH	1	6.7%	1	6.7%	2	0.000	1.000
	ALIVE	14	93.3%	14	93.3%	28		

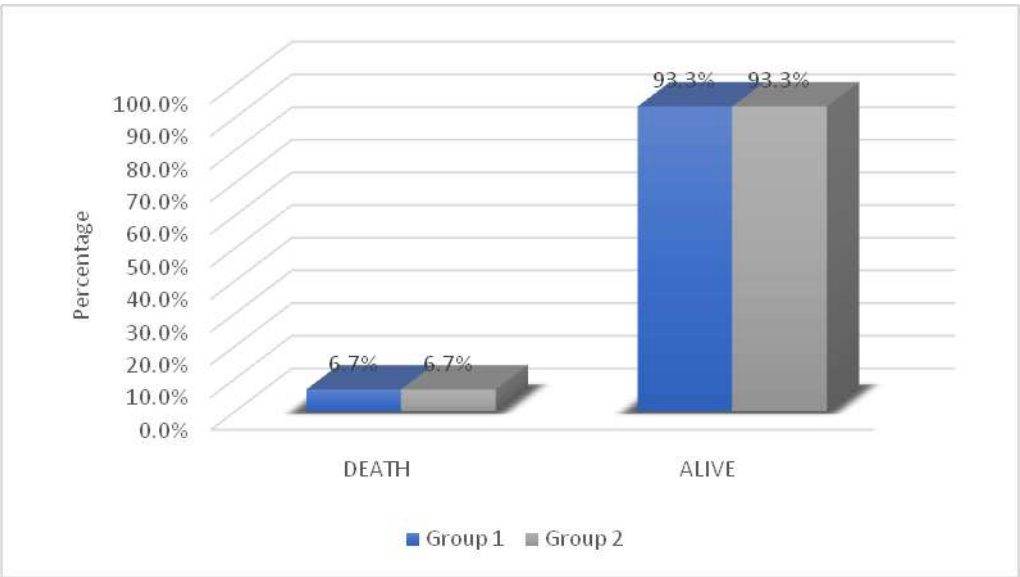


FIG 16: OUTCOME: COMPARISION OF NUMBER OF DEATHS

TABLE 17: ASSOCIATION OF DISEASE TYPE AND REMISSION

Group			REMISSION				Total	Chi-square value	p-value
			N		Y				
RTX	AAV	GPA	3	75.0%	10	90.9%	13	0.642	0.476
		MPA	1	25.0%	1	9.1%	2		
	Total		4	100.0%	11	100.0%	15		
CYC	AAV	GPA	5	100.0%	8	80.0%	13	1.154	0.524
		MPA	0	0.0%	2	20.0%	2		
	Total		5	100.0%	10	100.0%	15		

Among patients with GPA, 10assigned to rituximab (90%) and8 (80%) treated with cyclophosphamide reached the primary end point (P = 0.476). Among the patients with microscopicpolyangiitis, 1 of 2 in the rituximab group (50%) and 2 of 2 in the control group (100%) reached the primary end point.

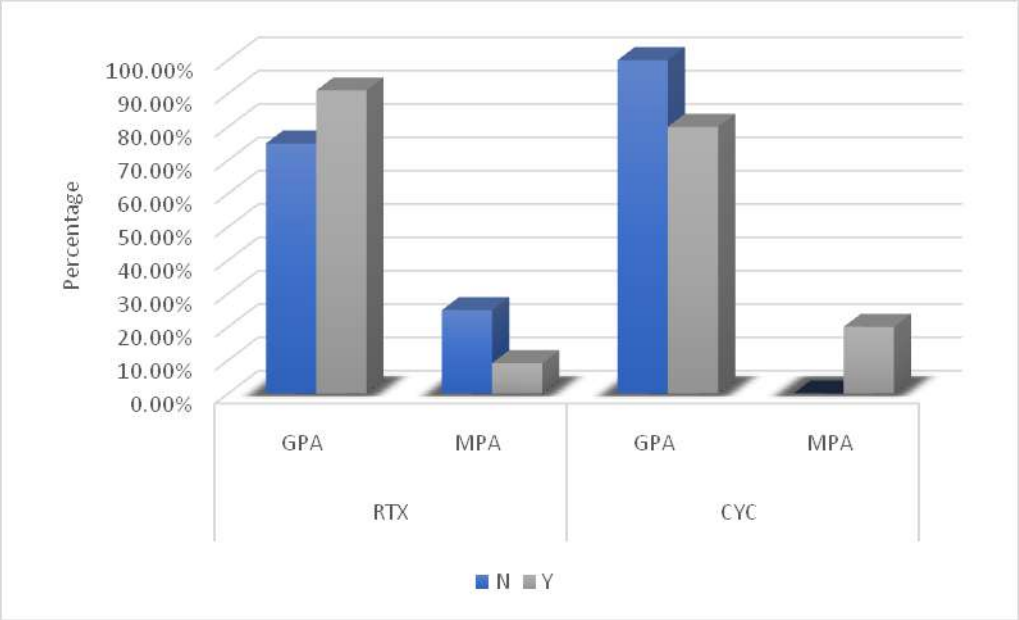


FIG 17: ASSOCIATION OF DISEASE TYPE AND REMISSION

TABLE 18: ASSOCIATION OF MAJOR RENAL DISEASE AT BASELINE ANDREMISSION

	RTX		CYC		T	p-value	**Difference**		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
CREAT_BASELINE	4.94	2.05	4.57	1.87	0.511	0.613	0.37	0.72	-1.10	1.84
Sixth Month	1.52	1.09	1.71	1.43	-0.387	0.702	-0.19	0.48	-1.17	0.80
Baseline-6 month	3.19	1.17	2.61	1.37	1.202	0.240	0.58	0.48	-0.41	1.57
EGFR_BASELINE	14.80	7.50	15.60	10.32	-0.243	0.810	-0.80	3.30	-7.55	5.95
Sixth Month	73.29	38.55	66.86	37.69	0.446	0.659	6.43	14.41	-23.19	36.04
Baseline-6 month	-57.86	32.54	-50.50	31.69	-0.606	0.550	-7.36	12.14	-32.31	17.59

All included patients had at least one major renal BVAS/WG item at baseline (i.e., urinary red-cell casts, biopsy-confirmed glomerulonephritis, or an increase in the baseline serum creatinine concentration of more than 30%).

Baseline renal function in the rituximab group was worse than in the control group [mean creatinine 4.9 $\pm$ SD 2.0 vs 4.57 $\pm$ SD 1.87] and estimated GFR14.8$\pm$ SD 7.5 vs 15.6$\pm$ SD10P = 0.04). However, the estimated GFR increased in parallel in the two groups during the first6 months (by 57.8 ml per minute/1.73 m^2 in the RTX group and 50.5 ml per minute/1.73 m^2 the control group), and the percentages of patients who reached the primary end point were not significantly different (11 of 15 patients in the rituximab group [73%] vs. 10 of 15 patients in the control group [66%] (P = 0.690).

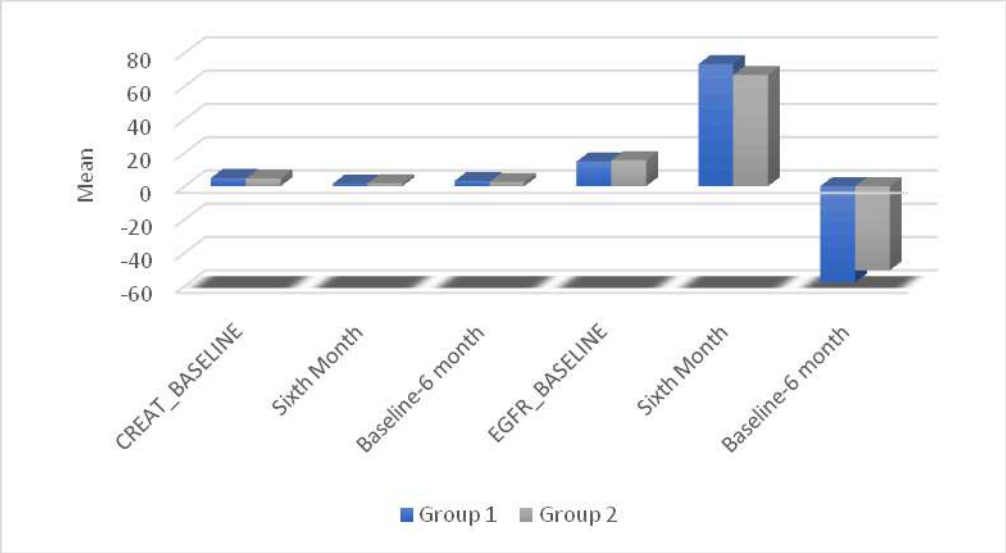


FIG 18: ASSOCIATION OF MAJOR RENAL DISEASE AT BASELINE AND REMISSION

TABLE 19: ALVEOLAR HEMORRHAGE AT BASELINE

		Group				Total	Chi-square value	p-value
		RTX		CYC				
HAEMOPTYSIS/ ALVEOLAR HEMORRHAGE	N	11	73.3%	12	80.0%	23	0.186	0.666
	Y	4	26.7%	3	20.0%	7		

4 (26.7%) patients in the RTX group had alveolar hemorrhage at baseline, as compared with 3(20%) in the control group.

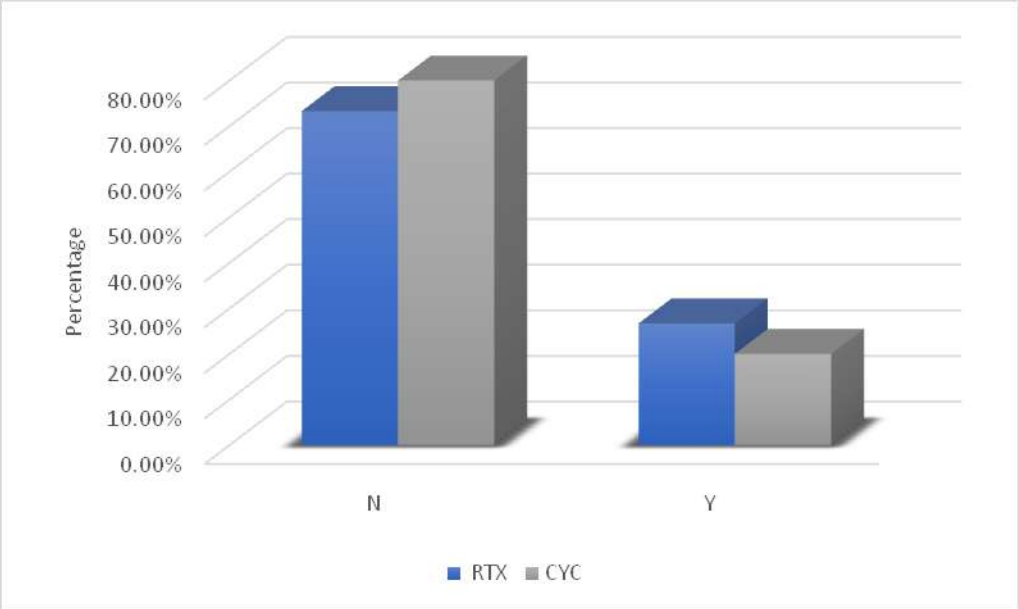


FIG 19: ALVEOLAR HEMORRHAGE AT BASELINE

TABLE 20: ASSOCAITION ALVEOLAR HEMORRHAGE AT BASELINE AND REMISSION

Group			REMISSION				Total	Chi-square value	p-value
			N		Y				
RTX	HAEMOPTYSIS/ ALVEOLAR HEMORRHAGE	N	2	50.0%	9	81.8%	11	1.519	0.516
		Y	2	50.0%	2	18.2%	4		
	Total		4	100.0%	11	100.0%	15		
CYC	HAEMOPTYSIS/ ALVEOLAR HEMORRHAGE	N	2	40.0%	1	90.0%	12	7.500	0.022
		Y	3	60.0%	**1**	10.0%	3		
	Total		5	100.0%	10	100.0%	15		

Among these patients, 2 (18.2%) in RTX reached the primary end point (P =0.516) as compared to none in CYC group (p= 0.022)

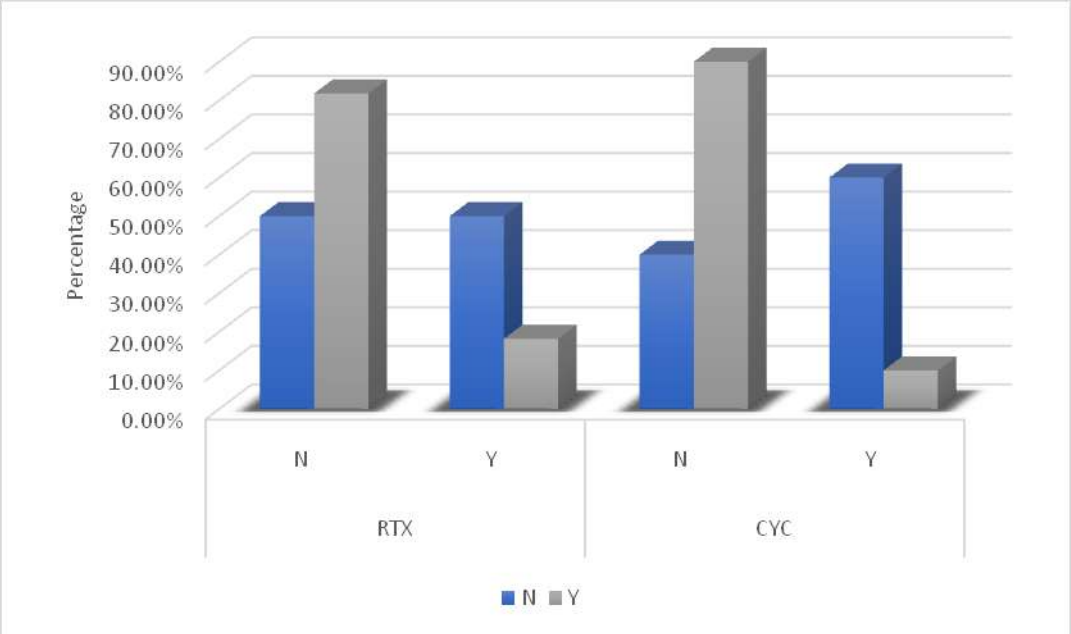


FIG 20: ALVEOLAR HEMORRHAGE AT BASELINE AND REMISSION

TABLE 21: COMPARISION OF ANCA RESPONSE

		Group				Total	Chi-square value	p-value
		RTX		CYC				
ANCA_TYPE	MPO	2	13.3%	2	13.3%	4	0.000	1.000
	PR3	13	86.7%	13	86.7%	26		
ANCA_ Baseline	+	15	100.0%	15	100.0%	30		
ANCA_3rd Month	+	8	57.1%	14	93.3%	22	5.179	0.023
	NEG	6	42.9%	1	6.7%	7		
ANCA_6th Month	+	6	42.9%	9	64.3%	15	1.292	0.256
	NEG	8	57.1%	5	35.7%	13		

42.9% in RTX and 6.7% in CYC group became ANCA negative by 3 months. 57.1 % in the RTX group and 35.7% in the control group became ANCA-negative by 6 months (P = 0.256).

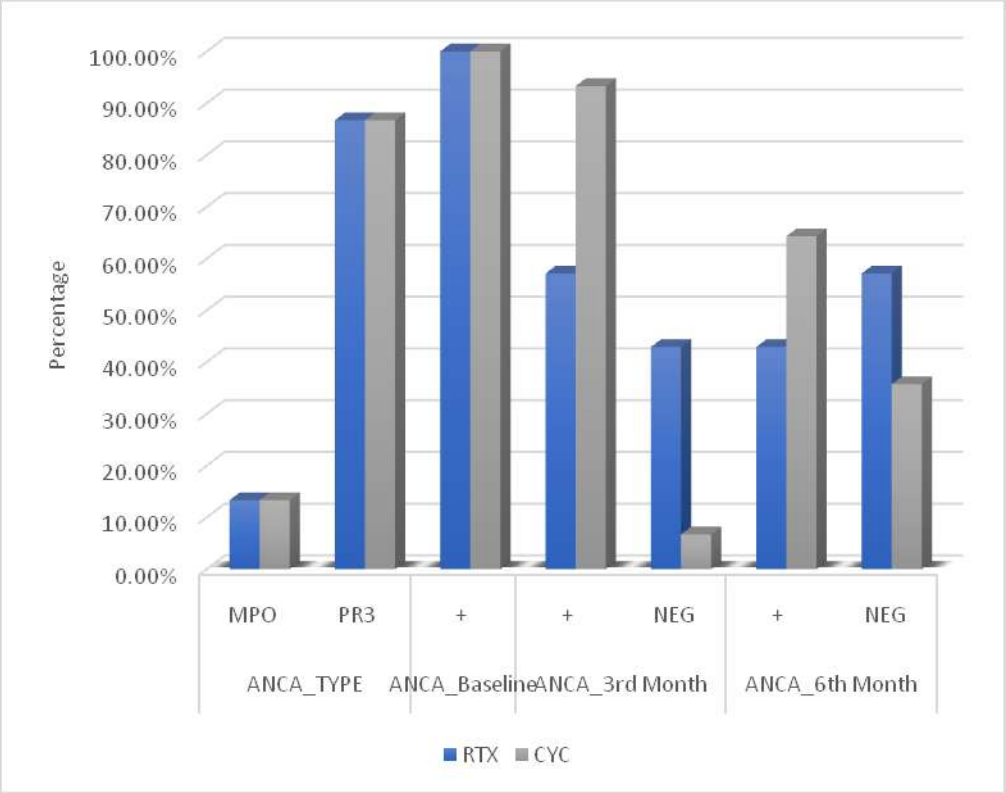


FIG 21: COMPARISION OF ANCA RESPONSE

TABLE 22: COMPARISION OF TYPE OF ANCA AND ANCA RESPONSE AT 3 MONTHS

Group			ANCA_3rd Month				Total	Chi-square value	p-value
			+		NEG				
RTX	ANCA TYPE	MPO	1	12.5%	1	16.7%	2	0.216	0.897
		PR3	7	87.5%	5	83.3%	12		
	Total		8	100.0%	6	100.0%	14		
CYC	ANCA TYPE	MPO	2	14.3%	0	0.0%	2	0.165	0.685
		PR3	12	85.7%	1	100.0%	13		
	Total		14	100.0%	1	100.0%	15		

This difference between the two treatment groups in loss of ANCA reactivity was in patients who were initially positive for proteinase3−ANCA. At 3 months, 5 patients (83.3 %) in the RTX group became negative for proteinase3−ANCA, as compared with only 1patientsin the CYC group (P =0.685).

In patients with MPO positivity, 1 patient became negative by 3 months in RTX group as compared to none in CYC group.

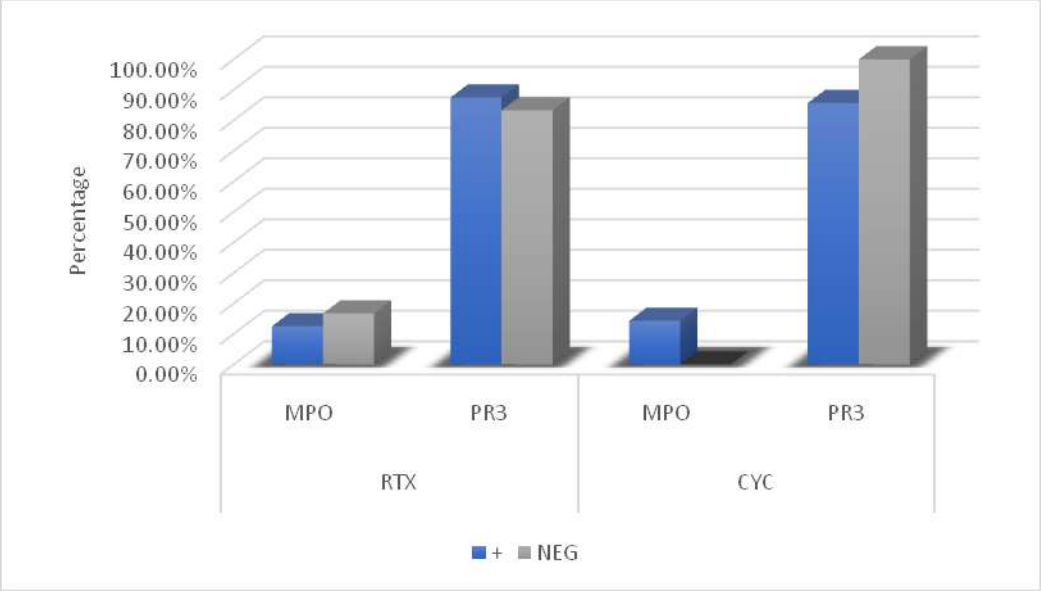


FIG 22: COMPARISION OF TYPE OF ANCA AND ANCA RESPONSE AT 3 MONTHS

TABLE 23: COMPARISION OF TYPE OF ANCA AND ANCA RESPONSE AT 6 MONTHS

Group			ANCA_6th Month				Total	Chi-square value	p-value
			+		NEG				
Group 1	ANCA TYPE	MPO	1	16.7%	1	12.5%	2	0.216	0.897
		PR3	5	83.3%	7	87.5%	12		
	Total		6	100.0%	8	100.0%	14		
Group 2	ANCA TYPE	MPO	1	11.1%	1	20.0%	2	0.385	0.825
		PR3	8	88.9%	4	80.0%	12		
	Total		9	100.0%	5	100.0%	14		

At 6 months, 7 patients (87.5%) became negative in PR3 group who received RTX (p= 0.897), as compared to 4 (80%) patients in CYC group (p = 0.825). In contrast, 1 patient in each RTX and CYC group became negative for myeloperoxidase−ANCA.

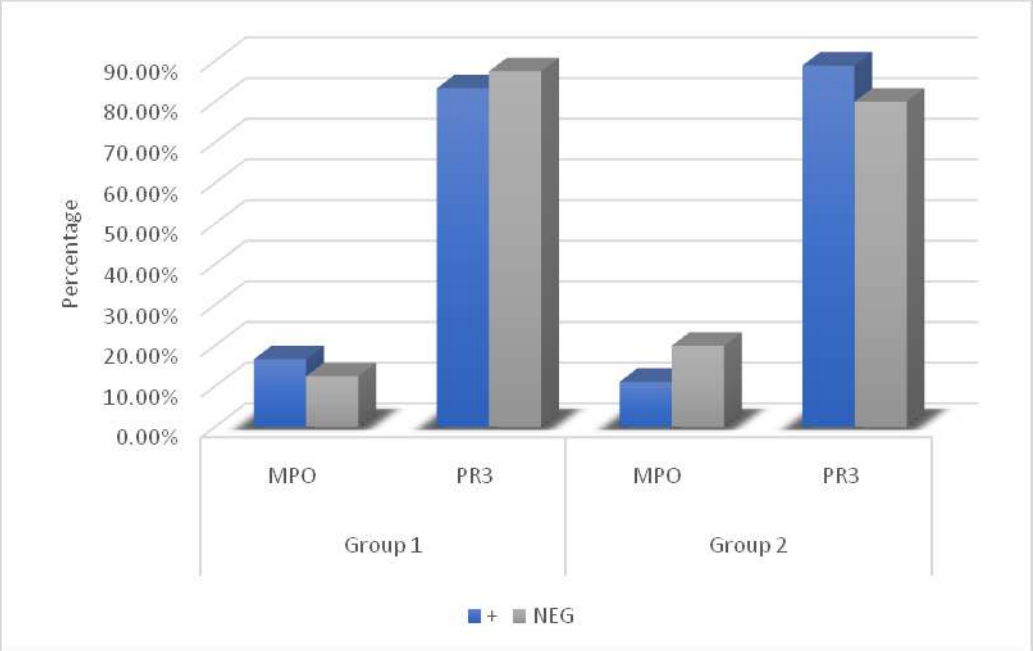


FIG 23: COMPARISION OF TYPE OF ANCA AND ANCA RESPONSE AT 6 MONTHS

III **EFFICACY ASSESSMENT**

- SECONDARY OUTCOMES:

1. Response rate at 6 weeks (BVAS < 50% baseline).
2. Remission at 6 months (BVAS=0 for 2 months by 6 months).
3. Time to remission (BVAS=0).
4. Change in Estimated glomerular filtration rate (e GFR)

TABLE 24: COMPARISION OF RESPONSE AT 6 WEEKS (BVAS < 50% baseline)

		Group				Chi-square value	p-value
		RTX		CYC			
BVAS <50% AT 6 WEEKS	Y	11	73.30%	9	60.00%	0.600	0.438
	N	4	26.60%	6	40.00%		

In RTX group 11 patients (73.3%) and 9 (60 %) patients in CYC group attained BVAS < 50% from baseline at 6 weeks (p = 0.438)

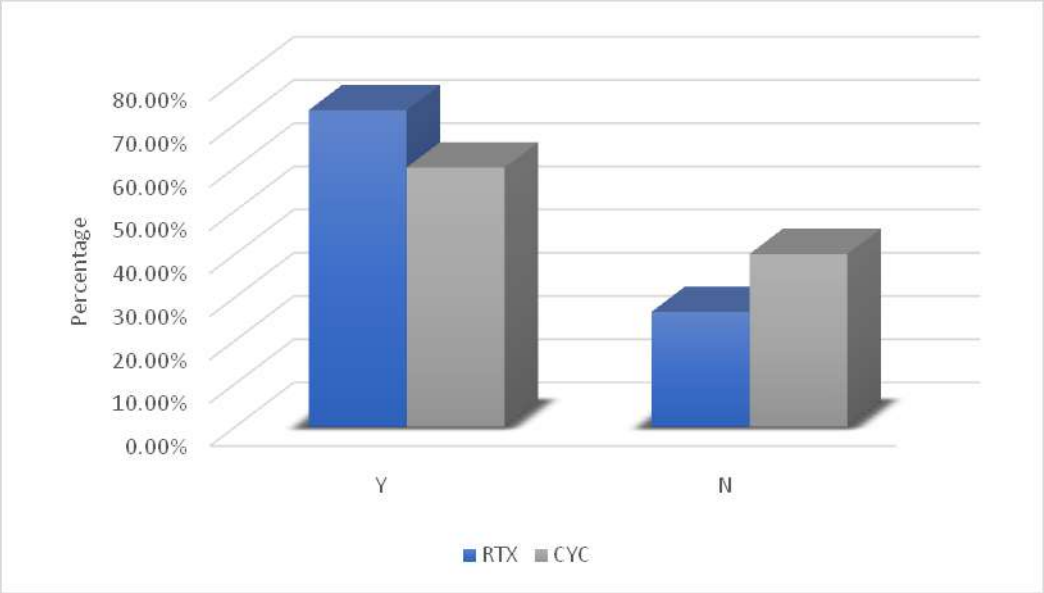


FIG 24: COMPARISION OF RESPONSE AT 6 WEEKS (BVAS < 50% baseline)

TABLE 25: COMPARISION OF REMISSION (BVAS=0 for 2 months by 6 months)

	RTX		CYC		p-value
	Number	Percentage	Number	Percentage	
BVAS =0 at baseline	0	0%	0	0%	-
BVAS=0 Second Month	6	40%	4	27%	0.432
BVAS =0 Sixth Month	10	67%	10	67%	-

Remission at 6 months (BVAS =0 for 2 months by 6 months) was seen in equal number of patients in both RTX and CYC group, i.e, 10 patients in each group 67%)

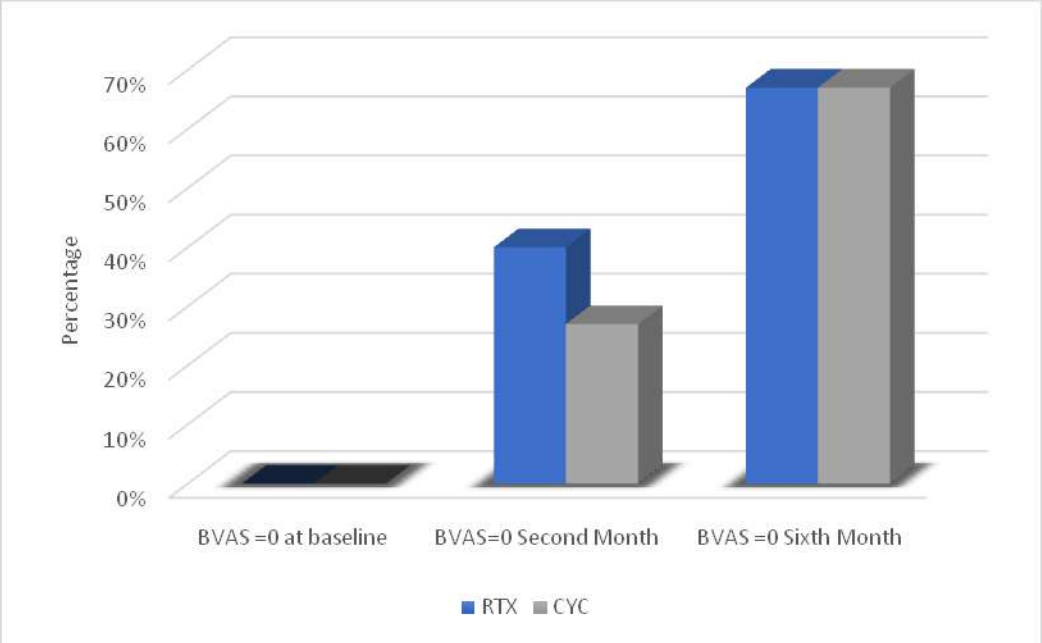


FIG 25: COMPARISION OF REMISSION (BVAS=0 for 2 months by 6 months)

TABLE 26: COMPARISION OF TIME TO REMISSION (BVAS=0)

BVAS	RTX		CYC		t	p-value	**Difference**		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
BVAS=0 TIME TO REMISSION	2.30	0.67	2.60	0.52	-1.116	0.279	-0.30	0.27	-0.86	0.26
BVAS < 50 % TIME TO REMISSION	1.67	1.24	1.86	1.35	-0.380	0.707	-0.19	0.49	-1.19	0.82

The median BVAS decreased from 20 at study entry to 0 at 2.3 months in the rituximab group and from 20 at study entry to 0 at 2.6 months in the control group.

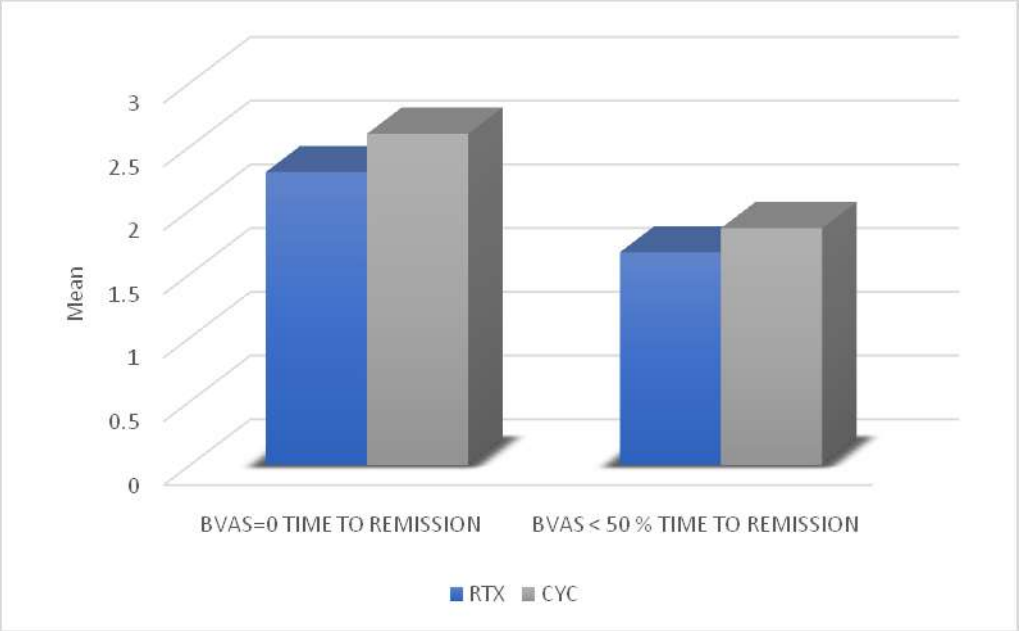


FIG 26: COMPARISION OF TIME TO REMISSION (BVAS=0)

TABLE 27: COMPARISION OF CHANGE IN EGFR

	RTX		CYC		t	p-value	**Difference**		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
CREAT_BASELINE	4.94	2.05	4.57	1.87	0.511	0.613	0.37	0.72	-1.10	1.84
Sixth Month	1.52	1.09	1.71	1.43	-0.387	0.702	-0.19	0.48	-1.17	0.80
Baseline-6 month	3.19	1.17	2.61	1.37	1.202	0.240	0.58	0.48	-0.41	1.57
EGFR_BASELINE	14.80	7.50	15.60	10.32	-0.243	0.810	-0.80	3.30	-7.55	5.95
Sixth Month	73.29	38.55	66.86	37.69	0.446	0.659	6.43	14.41	-23.19	36.04
Baseline-6 month	-57.86	32.54	-50.50	31.69	-0.606	0.550	-7.36	12.14	-32.31	17.59

Baseline renal function in the RTX group was worse than in the control group [mean creatinine 4.9 ± SD 2.0 vs 4.57 ± SD 1.87] and estimated GFR 14.8± SD 7.5 vs 15.6± SD10 P = 0.04). However, the estimated GFR increased in parallel in the two groups during the first6 months, i.e, by 57.8 ml per minute in the RTX group and 50.5 ml per minute in the control group (p= 0.550).

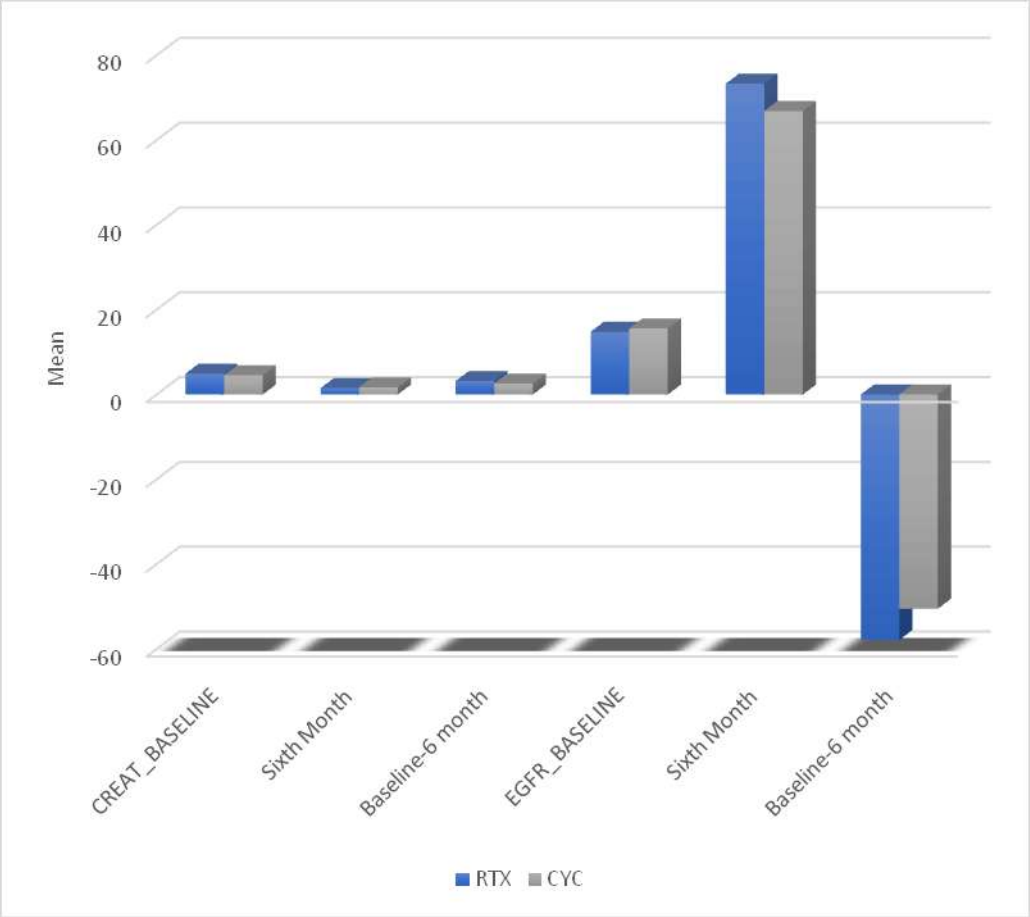


FIG 27: COMPARISION OF CHANGE IN EGFR

IV. ADVERSE EVENTS

TABLE 28: COMPARISION OF ADVERSE EVENTS

		Group				Total	Chi-square value	p-value
		RTX		CYC				
COMPLICATIONS	PANCYTOPENIA	1	6.7%	0	0.0%	1	4.000	0.406
	INFUSION RELATED REACTIONS	1	6.7%	0	0.0%	1		
	NONE	12	80.0%	12	80.0%	24		
	PANCYTOPENIA	0	0.0%	2	13.3%	2		
	SEPSIS	1	6.7%	1	6.7%	2		
Total		15	100.0%	15	100.0%	30		

There were no significant differences between the treatment groups in the numbers of total adverse events and serious adverse events. More episodes of pancytopenia in the control group 2 (13.3%) vs 1 (6.7%) were seen (p = 0.406). 1 (6.7%) mild infusion related reaction noted in RTX group. 1 (6.7%) in each group had sepsis related death.

No malignant conditions were detected in patients in 6 months.

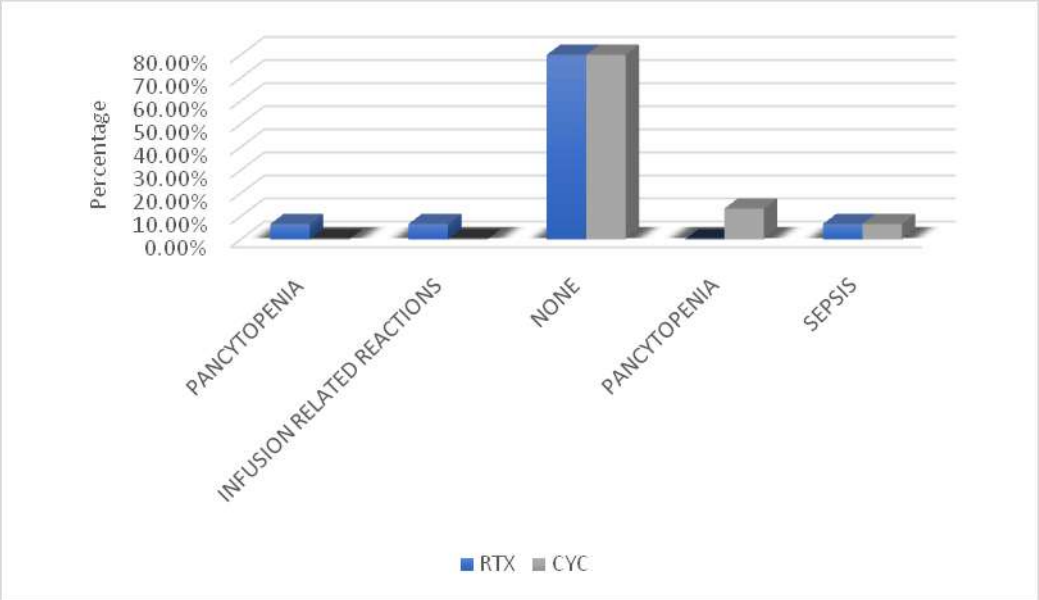


FIG 28: COMPARISION OF ADVERSE EVENTS

DISCUSSION

This two group randomized study was conducted in department of Nephrology, Dayanand Medical College and Hospital, Ludhiana, starting from 1st march 2019. 30 patients presenting with clinical features of ANCA associated vasculitis with renal involvement were included in this study. These patients were randomized into two groups. 1 group receiving Cyclophosphamide and other receiving Rituximab as induction therapy.

Among these patients, In baseline characteristics, mean age was 46±5. years in RTX group and 46.7 ± 5.97 in control group.

GPA can manifest in all age groups but commonly affects middle aged to elderly people with mean age of onset between 47 to 55 years in Western populations.

In a largest case series on GPA from India, which described clinical details and outcomes of 105 patients with GPA from PGI.[69] It seems to affect a relatively younger population in India compared to European and American populations. The mean age of presentation was 40 years which is about a decade earlier than in European and American populations.[70-73] Older Indian studies have noted the mean age of presentation to be between 32 to 42 years, but a recent study documented a mean age of 46 years, which is comparable to that of Western studies.[74-76]

The mean age at presentation in Asian populations varies from 40 to 65 years[77,78] Among Chinese, Korean and Taiwanese cohorts, the mean age at presentation was similar to that seen in Western populations.[79,80] However, Indian patients with GPA had earlier age of onset with mean age at presentation being 40 years. Age at presentation was highest among Japanese patients with mean age around 65 years.[81,82]

In a study by Mahr et al. 2012 in Europe [72], 54% Males and 46% females were involved. In a study by Holle et al 2011 in Germany[70] and Hoffman et al 1992 in USA [44], equal number (50%) of males and

females were involved. But in Indian study by Kumar et al. 2015 [74], female preponderance was seen 57% as compared to males 43%.

In largest Indian case series Among 105 patients 45 (42.86%) were males and 60 (57.14%) were females.[69] In our study, Female preponderance was seen in both groups 9 (60%) in RTX and 10 (66.7%) IN CYC group.

Constitutional symptoms including fever, weight loss and myalgia were seen in 86% of patients in RTX group and 93% of patients in CYC group.

In a study by Sharma et al [69], Constitutional symptoms were most common, seen in 80% of patients at presentation.

Cutaneous involvement was seen in 29.52% in a study by Sharma et al [69], similarly in our study, Skin involvement was in form of purpura, ulcers and gangrene. Purpura was seen in 20% patients in RTX and 13% patients in CYC group. Ulcers were present in 13.3 % patients in both groups.

Eye involvement was seen in 26% of patients in both groups in the form of conjunctivitis and scleritis. In a study by Sharma et al [69] eye involvement was observed in 40% of patients. In US population, frequency of eye involvement was seen in 32% of patients in a study by Hoffman et al[44] Ocular involvement was noted in 30%- 40% of patients in Asian cohorts, which was similar to that noted in European studies.

In a study by Sharma et al [69] and Kumar et al India [78],79%-80% of patients had ENT involvement at presentation, as compared to USA, where ENT involvement was seen in 92% of patients in a study by Hoffmann et al.[44] URT manifestations were noted in 79%- 91% of patients in various cohorts from Asia [83] except for the Chinese patients where the URT involvement was noted in only 50% of patients.[84] In our study, 66% patients in RTX group and 73% in CYC group had ENT involvement.

Pulmonary involvement was noted in 66%- 77% in studies from India[83] China and Korea, while the Japanese study showed higher frequency of pulmonary manifestations, seen in up to 85% of patients.

Lung involvement in Indian studies ranges from 50-68%[69,74] as compared to USA 75-85%.[44,71] In our study, 60 % patients had lung involvement in both groups, most common lung infiltrates seen in 40% and 46% in RTX and CYC group respectively. Cavities were seen in 13.3% of patients in both groups. Alveolar hemorrhage and hemoptysis seen in 26% in RTX group and 20% in CYC group similar in frequency as seen in study by Sharma et al.[69]

Nervous system involvement was seen in 6.7% of patients in both groups in our study, in the form of sensory peripheral neuropathy and Mononeuritis multiplex in CYC and RTX group respectively. In a study by Sharma et al[69] 26.67% and 11.43% of patients had central nervous and peripheral nervous system involvement, respectively. In a study by Hoffman et al [44], 9% and 5 % patients had PNS and CNS involvement at presentation. Similarly PNS involvement in 13 % and CNS in 5 % patients was seen in a study by stone et al.[71]

Gastrointestinal tract and cardiovascular involvement was not seen in any of Patients in both groups in our study.

Renal involvement was seen in all patients in this study. Hypertension and microscopic hematuria was seen in all patients in both groups. Pedal edema was seen in 46% and 33% of patients in RTX and CYC group respectively. Gross hematuria was seen in 13% of patients in RTX and 20% of patients in CYC group. Oliguria was seen in 26.7 % patients in both groups. In a study by Shobha et al [85], all patients with renal involvement had hematuria. Macroscopic hematuria was seen in11%and 90% had microscopic hematuria. Hypertension was present in 100% patients with renal disease. Mean creatinine of this subgroup at presentation was 4.5 mg/dl (range from 2 to10 mg/dl).

In our study mean serum creatinine seen in RTX group was 4.9 mg/dl (mean e GFR 14.8 ml/min/1.73 m^2) as compared to 4.57 mg/dl in CYC group with mean e GFR of 15.6 ml/min/1.73 m2. All patients underwent renal biopsy with most common finding pauci immune crescentric glomerulonephritis similarly as seen in study by Shobha et al.[85]

In our study, 86.7 % patients had GPA in both groups. Only minority of patients had MPA (13.3% in both groups). All patients had ANCA

positivity by immunoblot assay. Majority of patients having PR3 positivity (86.7%) as compared to MPO (13.3%). These findings were consistent with other Indian studies in which PR3 positivity was seen predominantly seen 62% as compared to MPO positivity 7% Sharma et al [69], Kumar et al.[74] This is in contrast to studies in USA by Stone et al[71] in which MPO positivity is observed equally or slightly more in frequency. Among Chinese and Japanese patients, MPO ANCA was the predominant subtype with up to 60% of patients having MPO positivity.[80-82]

In our study, 86.7 % patients had GPA in both groups. Only minority of patients had MPA (13.3% in both groups). After diagnosis of AAV, and documented renal involvement, BVAS score was calculated at baseline and weekly thereafter for 1st month and then monthly for next 6 months. Baseline mean BVAS score was 20.13 in RTX group and 20 in CYC group at presentation in our study. In study done by Sharma et al[69], The median BVAS score at presentation among all patients was 17.0. BVAS score was significantly higher among patients who expired compared to those who survived (20.0 vs. 16.0, P = 0.028). In a study by Jones RB [62], BVAS was 19/18 in both study groups. 2 patients (13.3%) had diagnosis of microscopic polyangiitis, and 13 (86.7%) had diagnoses of GPA in both groups. All patients in both groups had a new diagnosis. 15 patients were assigned to RTX, and 15 patients were assigned to CYC.

After randomization, the two groups received intravenous methylprednisolone (at a dose of 1 g) and the same oral glucocorticoid regimen (1 mg per kilogram per day initially, with a reduction to 5 mg per day at the end of 6 months). Patients in the rituximab group received premedication with 1g paracetamol and chlorpheniramine 10 mg IV followed by 4 doses of 350 mg/m2 of IV Rituximab once weekly for 4 weeks, for 4 consecutive weeks. These patients did not receive azathioprine to maintain remission. Patients in the control group received 3-6 doses of CYC 15 mg/kg, first 3 doses given at 2 weeks interval, following doses given every 3 weekly. Dose reduction according to creatinine > 3 mg/dl was done (12.5 - 10 mg/kg/pulse),

minimum for 3 months was given in 10 patients. CYC was switched to AZA (2mg/kg/day) after 3 months in 10 patients who achieved remission.

All patients received calcium and vitamin D supplementation, Proton pump inhibitor, PCP prophylaxis (Cotrimoxazole + Sulfamethoxazole). 13.3 % of patients required HD and PLEX in both groups.

Full clinical remission is indicated by complete absence of clinical disease activity using BVAS/WG: BVAS score 0 for 2 months. The absence of renal disease activity is indicated by stable or falling creatinine and the absence of red cell casts. Diagnosis of complete remission is supported by a normal C-reactive protein.

Partial remission (PR) was defined as clinically relevant improvement of disease activity without fulfilling the criteria for CR.

11 patients out of 15 (73.3%) in the RTX and 10 patients out of 15 (66.7%) in CYC group reached the primary end point. The proportion of patients who reached the primary end point was more in the rituximab group than in the control group, but the difference was not significant (P = 0.690). 11 patients treated with rituximab (73%) reached the secondary end point of disease remission while receiving less than 10 mg per day of prednisone, as compared with 10 patients in the control group (63%, P = 0.10). In a landmark study by Jones RB[62], Rituximab with Cyclophosphamide as induction therapy in ANCA-associated vasculitis was compared and it was found that Rituximab-based regimen was not superior to standard intravenous cyclophosphamide for severe ANCA-associated vasculitis.

In a landmark trial by Stone et al [63], which compared Rituximab to oral Cyclophosphamide, it was shown that Rituximab therapy was not inferior to daily cyclophosphamide treatment for induction of remission in severe ANCA-associated vasculitis. Among patients with Wegener's granulomatosis, 46 of 73 assigned to rituximab (63%) and 37 of 74 treated with cyclophosphamide (50%) reached the primary end point (P = 0.11). in our study, among patients with GPA, 10 assigned to rituximab (76%) and 8 (61%) treated with cyclophosphamide reached the primary end point (P = 0.476). Among the patients with microscopic

polyangiitis, 1 of 2 in the rituximab group (50%) and 2 of 2 in the control group (100%) reached the primary end point. All included patients had at least one major renal BVAS/WG item at baseline (i.e., urinary red-cell casts, biopsy-confirmed glomerulonephritis, or an increase in the baseline serum creatinine concentration of more than 30%).

In landmark study by Stone [63], baseline renal function was 53.8ml per minute vs. 68.9 ml per minute in RTX and CYC group respectively, but the estimated creatinine clearance increased in parallel in both groups. In our study, Baseline renal function in the rituximab group was worse than in the CYC group [mean creatinine 4.9 $\pm$ SD 2.0 vs 4.57 $\pm$ SD 1.87] and estimated GFR 14.8 $\pm$ SD 7.5 vs 15.6 $\pm$ SD10 P = 0.04). However, the estimated GFR increased in parallel in both groups during the first 6 months (by 57.8 ml per minute in the RTX group and 50.5 ml per minute in the control group),and the percentages of patients who reached the primary end point were not significantly different (11 of 15 patients in the rituximab group [73%] vs. 10 of 15 patients in the control group [66%], P = 0.690).4 (26.7%) patients in the RTX group had alveolar hemorrhage at baseline, as compared with 3 (20%) in the control group. Among these patients, 2 (18.2%) in RTX reached the primary end point (P =0.516) as compared to 1in CYC group (p= 0.022) 42.9% in RTX and 6.7% in CYC group became ANCA negative by 3 months. 57.1 % in the RTX group and 35.7 % in the control group became ANCA-negative by 6 months (P = 0.256). ANCA negativity was observed in 47% of patients in RTX group as compared to 24% in CYC group in landmark trial by Stone.[63]

There were no significant differences between the treatment groups in the numbers of total adverse events and serious adverse events. More episodes of pancytopenia in the control group 2 (13.3%) vs 1 (6.7%) were seen(p = 0.406). 1 (6.7%) mild infusion related reaction noted in RTX group. 1 (6.7%) in each group had sepsis related death.

We anticipated lower rates of adverse events in the rituximab group, but we did not observe major differences between the two groups in overall adverse events. There are several possible reasons for this finding. First, adverse events, by their definition, include both disease

and treatment complications, including those related to glucocorticoid use. Second, 6 months may have been too short a period in which to detect some of the cyclophosphamide-associated adverse events(e.g., infertility). Third, rigorous monitoring of all patients in our study may have reduced the incidence of cyclophosphamide-induced leucopenia, which may occur in clinical practice if blood counts are not checked every 2 weeks

Patients who expired had a higher BVAS score compared to patients who survived, indicating that BVAS score at presentation is useful in determining severity of disease and helps in determining prognosis, consistent with findings by Sharma et al.[69]

In our patients, sepsis was the cause of mortality in both groups. This was consistent with that reported by Hoffmann et al [44] and Reinhold-Keller et al.[73] The most common complication noted during the Study by Shobha et al [85] was infections in 30 (68%) patients followed by blood dyscrasias in 22 (50%) patients.

It is a known fact that there is an important unmet need for safer and more effective therapies in patients with ANCA associated vasculitis, especially those at highest risk for treatment toxicity and death, such as elderly patients and those with severe renal dysfunction.

In our study the efficacy of a rituximab-based regimen versus a conventional cyclophosphamide regimen as remission-induction therapy for ANCA-associated renal vasculitis was investigated. The rituximab-based regimen was comparable to conventional cyclophosphamide regimen (73% VS 67%). Both treatment groups had high rates of remission. Remission rates were not superior in the rituximab group.

These rates are similar to those reported in previous studies.[62,63]

Renal involvement was the predominant manifestation of disease, and objective measurements such as creatinine levels were used to assess renal function. Adherence to the corticosteroid-reduction protocol was good.

Only 3 survivors in the rituximab group did not have a sustained remission. Uncontrolled studies have shown an efficacy rate of 80 to

90% with rituximab treatment in refractory ANCA associated vasculitis.[86-90] In this study, the sustained responses in patients in the rituximab group were probably attributable to a long-lasting effect of early rituximab treatment. Duration of remission beyond 6 months or the value of repeated administration of rituximab to maintain remission was not assessed.

Cyclophosphamide is a recommended component of induction therapy for ANCA-associated vasculitis with major organ involvement[91,92] however, its use is complicated by infections, cancer, and infertility [93,94]. In order to minimize cyclophosphamide toxicity, treatment regimens have been modified by switching to an alternative drug as azathioprine for remission maintenance or by using pulsed therapy ; both approaches reduce the cumulative exposure to cyclophosphamide.[95]

The use of rituximab can further reduce exposure to cyclophosphamide. Rituximab has not been associated with a significant increase in infectious complications when used in combination with methotrexate for the treatment of rheumatoid arthritis[96] or with chemotherapy for the treatment of non-Hodgkin's lymphoma.[97] Furthermore the use of rituximab, unlike cyclophosphamide, rarely results in profound leukopenia. However, in this study, the rituximab-based regimen was not associated with lower rates of early severe adverse events than the cyclophosphamide-based regimen, and no difference in safety was observed. Older age and a lower GFR are strong predictors of death among patients with ANCA-associated vasculitis.[98]

Mortality was same in the two treatment groups and was consistent with the 7% rate of death reported in a large cohort study involving patients with ANCA-associated renal vasculitis [98], as well as the rates of death in other trials involving patients with ANCA-associated renal vasculitis[49,66] In our study both deaths were attributed to infection, and the majority of deaths occurred early in treatment (before 3 months). Up to 6 weeks from study entry, the two groups received the same Glucocorticoid regimens. Thus, any advantage of rituximab is with the

avoidance of large cumulative doses of cyclophosphamide and maintenance immunosuppression.

Rituximab exerts its effect predominantly through B-cell depletion. Part of cyclophosphamide's therapeutic effect may be mediated through control of B-cell auto reactivity by means of B-cell suppression.[99]

B-cell−derived ANCA is implicated in the pathogenesis of vasculitis, and ANCA negativity after induction therapy is associated with a reduced risk of relapse.[100] The B-cell depletion with rituximab was associated with a clinical response and all patients in the rituximab group became ANCA-negative by 6 months. The rate of ANCA negativity in this study was higher than that observed with cyclophosphamide regimens in previous studies.[49] However, the disruption of other B-cell functions, including antigen presentation and T-cell co-stimulation, may also contribute to the therapeutic mechanism of rituximab.

In conclusion, both Rituximab and Cyclophosphamide can have comparable efficacy as induction agent for AAV with Rituximab having advantage of lesser side effects including leucopenia and infertility, but higher cost. Whereas Cyclophosphamide have been established as standard of care for induction in AAV, but its toxicity limits its use particularly in younger population.

SUMMARY AND CONCLUSION

- This is an open-label, two-group, parallel design, randomized study of 30 patients of ANCA vasculitis comparing a Rituximab based regimen with IV Cyclophosphamide regimen in the treatment of active 'generalised' AAV.
- This study was conducted in Department of Nephrology at DMCH Ludhiana from 1st march 2019. All the patients presenting with features of ANCA associated vasculitis with renal involvement from will be included in this study
- 30 patients were included in the study. 15 patients were included in RTX group and 15 were included in CYC group for induction. They were followed up for 6 months.
- Mean age at presentation was 46.4±5. years in RTX group and 46.7 ± 5.97 in CYC group.
- Female preponderance was seen in both groups 9 (60%) in RTX and 10 (66.7%) in CYC group.
- Most common symptoms at presentation were constitutional symptoms including fever arthalgias, myalgias and weight loss
- Upper respiratory tract was involved in 60% patients in RTX group and 66.7 % in CYC group). Majority of patients had paranasal sinus involvement.
- 40 % patients in RTX group and (46.7%) in CYC group had pulmonary involvement in the form of cavities, infiltrates and DAH
- Renal symptoms were macroscopic hematuria, pedal edema, oliguria.
- Urinary findings at baseline were microscopic hematuria and proteinuria (100% patients in both groups).
- Mean serum creatinine seen in RTX group was slightly higher (4.9 mg/dl)as compared to CYC group(4.5mg/dl).
- All patients underwent renal biopsy with most common finding pauci immune crescentric glomerulonephritis

- All patients had ANCA positivity by immunoblot assay. Majority of patients having PR3 positivity (86.7%) as compared to MPO (13.3%).
- Mean BVAS score was 20.13 in RTX group and 20 in CYC group at presentation.
- Majority of patients had diagnosis of GPA.
- 13.3 % of patients required HD and PLEX in both groups

TREATMENT OUTCOMES:

- All patients in both groups received methylprednisolone pulse (1g IV), followed by prednisolone 1mg/kg/day.
- It was tapered to 5 mg/day at the end of 6 months in 10 patients in both groups
- RTX was given in 4 doses once weekly infusion for 4 doses.
- Patients in CYC group received 3-6 doses of CYC 15 mg/kg, first 3 doses given at 2 weeks interval, following doses given every 3 weekly. Dose reduction according to creatinine > 3 mg/dl was done (12.5 - 10 mg/kg/pulse)
- CYC was switched to AZA (2mg/kg/day) after 3 months in those patients who achieved remission
- All patients received calcium and vitamin D supplementation, Proton pump inhibitor , PCP prophylaxis (Cotrimoxazole + Sulfamethoxazole)
- 11 patients out of 15 (73.3%) in the RTX and 10 patients out of 15 (66.7%) in CYC group reached the primary end point. but the difference was not significant (P = 0.690).
- 11patients treated with rituximab (73%) reached the secondary end point of disease remission while receiving less than 10 mg per day of prednisone, as compared with 10 patients in the CYC group (63%, P = 0.10).
- Among patients with GPA, 10 assigned to rituximab (90%) and 8 (80%) treated with cyclophosphamide reached the primary end point (P = 0.476).

- Among the patients with microscopic polyangiitis, 1 of 2 in the rituximab group (50%) and 2 of 2 in the control group (100%) reached the primary end point.
- Estimated GFR increased in parallel in the two groups during the first 6 months (by 57.8 ml per minute in the RTX group and 50.5 ml per minute in the control group), and the percentages of patients who reached the primary end point were not significantly different in both groups.
- 57.1 % in the RTX group and 35.7 % in the control group became ANCA-negative by 6 months (P = 0.256).
- There were no significant differences between two groups in the number of total adverse events and serious adverse events. More episodes of pancytopenia in the control group 2 (13.3%) vs 1 (6.7%) were seen(p = 0.406). 1 (6.7%) mild infusion related reaction noted in RTX group.
- 1 (6.7%) in each group had sepsis related death.
- In secondary outcomes, in RTX group 11 patients (73.3 %) and 9 (60 %) patients in CYC group attained BVAS < 50% from baseline at 6 weeks (p = 0.438)
- Remission at 6 months (BVAS =0 for 2 months by 6 months) was seen in equal number of patients in both RTX and CYC group, i.e, 10 patients in each group 67%)
- The median time to remission was 2.3 months in the RTX group and 2.6 months in the CYC group.

In conclusion, this study show that median age of presentation is younger as compared to western population, with predominant c-ANCA (PR3 positivity in our population. RTX as induction therapy for AAV is as effective as CYC with no incidence of increased adverse effects.

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S.no.	Name	Group	SEX	Age	MRD No.	constitutional symptoms				CUTANEOUS					
						WEIGHT LOSS	ARTHRALGIA	FEVER	MYALGIA	INFARCT	PURPURA	ULCER	GANGRENE	OTHER	MOUTH ULCERS
1	AK	1	F	45	701438	Y	N	Y	Y	N	N	N	N	N	N
2	SG	2	F	48	362055	Y	N	N	N	N	N	N	N	N	N
3	KK	2	F	47	537920	N	N	Y	Y	N	N	N	N	N	N
4	R	2	F	42	724791	Y	Y	N	N	N	N	N	N	N	N
5	SS	2	M	36	517992	Y	N	Y	Y	N	N	Y	N	N	N
6	SA	1	M	46	776746	N	N	N	N	N	N	N	N	N	N
7	R	1	F	48	835922	N	Y	Y	Y	N	Y	N	N	N	Y
8	AK	2	F	58	847888	Y	N	Y	N	N	Y	N	N	N	N
9	GS	1	M	46	833000	N	N	N	N	N	N	N	N	N	Y
10	HK	2	F	43	574016	N	N	Y	N	N	N	N	N	N	N
11	SK	1	F	38	668952	Y	Y	Y	Y	N	N	N	N	N	N
12	DG	2	M	47	725323	N	N	N	N	N	N	N	N	N	Y
13	BA	2	M	46	447039	N	N	N	Y	N	N	N	N	N	N
14	RK	1	M	46	537920	N	N	Y	Y	N	N	Y	N	N	N
15	GS	1	M	44	674684	N	N	Y	N	N	N	N	N	N	N
16	GK	2	F	52	496160	Y	Y	Y	N	N	N	N	N	N	N
17	SK	2	F	48	434127	Y	Y	N	N	N	N	Y	N	N	N
18	PK	2	F	56	567664	Y	Y	Y	N	N	N	N	N	N	N
19	WM	2	M	42	463370	N	N	N	Y	N	N	N	N	N	N
20	AB	1	F	48	635957	Y	Y	N	N	N	Y	N	N	N	N
21	SS	1	M	50	763754	Y	N	Y	Y	N	N	Y	N	N	N
22	KS	1	F	51	80709	Y	Y	Y	N	N	N	N	N	N	N
23	SK	1	F	38	849366	Y	Y	N	N	N	N	N	N	N	N
24	AB	1	F	50	692657	Y	Y	Y	N	N	N	N	N	N	N
25	KD	2	M	44	770073	N	N	Y	Y	N	N	N	N	N	N
26	K	1	M	42	579757	N	N	Y	N	N	N	N	N	N	N
27	AB	2	F	40	682657	Y	Y	Y	Y	N	N	N	N	N	N
28	JK	1	F	58	480614	Y	N	Y	N	N	Y	N	N	N	N
29	SK	1	F	47	755692	Y	N	Y	N	N	N	N	N	N	N
30	AK	2	F	52	428513	N	Y	Y	N	N	Y	N	N	N	N

S.no.	Name	MUCOUS MEMBRANES/ EYES							EN		
		GENITAL ULCERS	ADNEXAL INFL.	PROPTOSIS	SCLERITIS	CONJUCTIVITIs ETC.	BLURRED	RETINAL EXUDATES	BLOODY NASAL DISCHARGE/ CRUSTING/ULCERS	SINUS INVOLVEMENT	SWOLLEN SALIVARY GLANDS
1	AK	N	N	N	N	N	N	N	N	Y	N
2	SG	N	N	N	N	N	N	N	N	N	N
3	KK	N	N	N	N	N	N	N	N	Y	N
4	R	N	N	N	N	N	N	N	Y	N	N
5	SS	N	N	N	N	N	N	N	N	N	N
6	SA	N	N	N	N	N	N	N	N	N	N
7	R	N	N	N	Y	N	N	N	Y	Y	N
8	AK	N	N	N	N	Y	N	N	N	N	N
9	GS	N	N	N	N	Y	N	N	N	N	N
10	HK	N	N	N	N	Y	N	N	N	Y	N
11	SK	N	N	N	N	N	N	N	N	Y	N
12	DG	N	N	N	N	N	N	N	N	N	N
13	BA	N	N	N	N	N	N	N	N	N	N
14	RK	N	N	N	N	N	N	N	N	N	N
15	GS	N	N	N	Y	N	N	N	Y	N	N
16	GK	N	N	N	N	N	N	N	N	N	N
17	SK	N	N	N	N	N	N	N	N	N	N
18	PK	N	N	N	N	Y	N	N	Y	Y	N
19	WM	N	N	N	N	N	N	N	Y	N	N
20	AB	N	N	N	N	Y	N	N	N	N	N
21	SS	N	N	N	N	N	N	N	N	N	N
22	KS	N	N	N	N	N	N	N	Y	Y	N
23	SK	N	N	N	N	N	N	N	Y	Y	N
24	AB	N	N	N	N	N	N	N	Y	N	N
25	KD	N	N	N	N	N	N	N	N	N	N
26	K	N	N	N	N	N	N	N	N	Y	N
27	AB	N	N	N	N	N	N	N	N	Y	N
28	JK	N	N	N	N	N	N	N	N	N	N
29	SK	N	N	N	N	N	N	N	N	N	N
30	AK	N	N	N	Y	N	N	N	Y	Y	N

S.no.	Name	ENT			CVS	GIT	PULMONARY			
		SUBGLOTTIC INFL.	CONDUCTIVE DEAFNESS	SENSORINEURAL DEAFNESS	PERICARDITIS	MESENTERIC ISCHEMIA	PLEURISY	NODULES/CAVITY	INFILTRATES	ENDOBRONCHIAL INVOLVEMENT
1	AK	N	N	N	N	N	N	N	N	N
2	SG	N	N	N	N	N	N	N	N	N
3	KK	N	N	N	N	N	N	N	N	N
4	R	N	N	Y	N	N	N	N	Y	N
5	SS	N	N	N	N	N	N	N	N	N
6	SA	N	N	N	N	N	N	N	N	N
7	R	N	N	Y	N	N	N	Y	Y	N
8	AK	N	Y	N	N	N	Y	N	Y	N
9	GS	N	N	N	N	N	Y	N	N	N
10	HK	N	N	N	N	N	N	N	Y	N
11	SK	N	Y	N	N	N	N	N	Y	N
12	DG	N	N	N	N	N	N	N	N	N
13	BA	N	N	N	N	N	N	N	N	N
14	RK	N	N	N	N	N	N	N	N	N
15	GS	N	N	N	N	N	N	N	N	N
16	GK	N	N	N	N	N	N	Y	N	N
17	SK	N	N	N	N	N	N	N	Y	N
18	PK	N	N	N	N	N	Y	N	Y	N
19	WM	N	N	N	N	N	N	N	N	N
20	AB	N	N	N	N	N	N	N	Y	N
21	SS	N	N	N	N	N	N	N	N	N
22	KS	N	N	Y	N	N	N	N	Y	N
23	SK	Y	N	N	N	N	N	Y	N	N
24	AB	N	N	N	N	N	N	N	Y	N
25	KD	N	N	N	N	N	N	N	N	N
26	K	N	N	N	N	N	N	N	N	N
27	AB	N	N	N	N	N	N		Y	N
28	JK	N	N	N	N	N	Y	N	Y	N
29	SK	N	N	N	N	N	N	N	N	N
30	AK	N	N	Y	N	N	N	Y	Y	N

S.no.	Name			RENAL					NERVOUS S		
		HAEMOPTYSIS/ ALVEOLAR HEMORRHAGE	RESPIRATORY FAILURE	PEDAL EDEMA	OLIGURIA	HYPERTENSION	PROTEINURIA	GROSS HAEMATURIA	MENINGITIS	CORD LESION	STROKE
1	AK	Y	N	N	N	Y	Y	N	N	N	N
2	SG	Y	N	N	N	Y	Y	N	N	N	N
3	KK	N	N	N	N	Y	Y	N	N	N	N
4	R	N	Y	Y	Y	Y	Y	Y	N	N	N
5	SS	N	N	N	N	Y	Y	N	N	N	N
6	SA	N	N	N	N	Y	Y	N	N	N	N
7	R	N	N	Y	Y	Y	Y	N	N	N	N
8	AK	Y	N	Y	N	Y	Y	Y	N	N	N
9	GS	N	N	N	N	Y	Y	N	N	N	N
10	HK	N	N	N	N	Y	Y	N	N	N	N
11	SK	N	N	N	N	Y	Y	N	N	N	N
12	DG	N	N	N	N	Y	Y	N	N	N	N
13	BA	N	N	N	N	Y	Y	N	N	N	N
14	RK	N	N	N	N	Y	Y	N	N	N	N
15	GS	N	N	N	N	Y	Y	Y	N	N	N
16	GK	N	N	Y	Y	Y	Y	N	N	N	N
17	SK	N	N	N	N	Y	Y	N	N	N	N
18	PK	N	N	Y	Y	Y	Y	N	N	N	N
19	WM	N	N	N	N	Y	Y	N	N	N	N
20	AB	Y	N	Y	N	Y	Y	N	N	N	N
21	SS	N	N	N	N	Y	Y	Y	N	N	N
22	KS	N	N	Y	Y	Y	Y	N	N	N	N
23	SK	Y	Y	Y	Y	Y	Y	N	N	N	N
24	AB	N	N	Y	Y	Y	Y	N	N	N	N
25	KD	N	N	N	N	Y	Y	N	N	N	N
26	K	N	N	Y	N	Y	Y	N	N	N	N
27	AB	N	N	N	N	Y	Y	N	N	N	N
28	JK	Y	Y	Y	N	Y	Y	N	N	N	N
29	SK	N	N	N	N	Y	Y	N	N	N	N
30	AK	Y	Y	Y	Y	Y	Y	Y	N	N	N

S.no.	Name	YSTEM			HEMOGLOBIN												
		CRANIAL NERVE PALSY	SPN	M.M.M	BASELINE	1st week	2nd week	3rd week	First Month	Second Month	Third Month	Fourth Month	Fifth Month	Sixth Month	BASELINE	1st Week	2nd week
1	AK	N	N	N	9.3	9.4	9.3	9.2	9	9.2	9.5	9.5	9.5	9.5	7400	8900	8400
2	SG	N	N	N	9.4	9.4	9.3	9.4	9.4	9.2	9.5	9.5	9.4	9.4	8900	9000	8800
3	KK	N	N	N	9.3	9.3	9.2	9	9	8	8.8	8.4	8.6	8.6	8000	9000	9100
4	R	N	Y	N	8.5	8.5	8.6	8.8	8.6	8.7					12000	18000	13000
5	SS	N	N	N	13	13	13	13.3	13.3	14	13.8	14	14.2	14	4000	9800	9900
6	SA	N	N	N	9.1	9.1	9	9.2	9.2	9.5	9.4	9.2	9.5	9.4	12000	10000	9800
7	R	N	N	Y	9.6	9.6	9.5	9.7	9.7	9.5	9.8	10	9.8	10	10000	12000	9800
8	AK	N	N	N	9.3	9.3	9.2	9.4	9.4	9.4	9.2	9.4	9.6	9	7840	8700	8500
9	GS	N	N	N	11	11	10.8	10.7	10.7	10.6	11	11.6	11.4	12	10600	9950	8900
10	HK	N	N	N	9.2	9.2	9	9.2	9.2	9	9.3	9.2	9.4	9.3	9200	8900	8700
11	SK	N	N	N	9	9	9	9.2	9.2	9.2	9.5	9.5	9.4	9.2	11,000	10,000	9,800
12	DG	N	N	N	11	11	10.5	10.7	10.7	10.6	11	11.6	11.4	12	10500	8000	7600
13	BA	N	N	N	9.1	9.1	9	9.2	9.2	9.5	9.4	9.2	9.5	9.4	12000	11500	9800
14	RK	N	N	N	9.4	9.4	9.4	9.5	9.5	9.9	10	10	10.2	10.2	9980	10000	9900
15	GS	N	N	N	9.4	9.4	9.6	9.8	9.8	9.2	9	9.5	9.3	9.2	11000	9700	8700
16	GK	N	N	N	9.5	9.5	9.4	9.6	9.6	9.4	9.3	9.1	9.2	9.5	9000	8500	8700
17	SK	N	N	N	9.6	9.6	9.4	9.5	9.5	9.8	10	10.5	10	10.5	18,000	15,000	12,000
18	PK	N	N	N	9.4	9.4	9.4	9.2	9.2	8.5	9	8.4	8.7	8.8	9800	11000	12000
19	WM	N	N	N	9.4	9.4	9.5	9.8	9.8	9.2	8.5	8.8	8.5	8.7	9800	9700	8690
20	AB	N	N	N	9.6	9.5	9.4	9.5	9.5	9.8	10	10.5	10	10.5	28,000	22,000	14,000
21	SS	N	N	N	13	13	13.2	13.3	13.3	14	13.8	14	14.2	14	9750	9500	9700
22	KS	N	N	N	9.4	9.4	9.4	9.2	9.2	9.5	9	9.4	9.7	10	12500	11000	9800
23	SK	N	N	N	8.5	8.5	8.5	8.8	8.8	8.7					11800	14000	13000
24	AB	N	N	N	9.5	9.5	9.4	9.6	9.6	8	8.8	8.4	8.6	8.6	8870	5670	5800
25	KD	N	N	N	9.4	9.4	9.2	9.5	9.5	9.9	10	10	10.2	10.2	9980	10000	9800
26	K	N	N	N	9.2	9.2	9	9.2	9.2	9.2	9.2	9	8.8	9	9900	9800	8900
27	AB	N	N	N	9	9	9	9.2	9.2	9.2	9.5	9.5	9.4	9.2	10,000	9,890	9,300
28	JK	N	N	N	9.3	9.3	9.3	9.4	9.4	9.4	9.2	9.4	9.6	9	7840	8700	9000
29	SK	N	N	N	9.4	9.4	9.2	9.4	9.4	9.2	9.5	9.5	9.4	9.4	9800	9900	9700
30	AK	N	N	N	10	10	10	9.8	9.8	9.5	9.7	9.6	9.8	10	11000	12000	10000

S.no.	Name	TLC							PLATELETS							
		3rd Week	First Month	Second Month	Third Month	Fourth Month	Fifth Month	Sixth Month	BASELINE	1st Week	2nd week	3rd Week	First Month	Second Month	Third Month	Fourth Month
1	AK	8700	8500	8700	10000	5600	4000	3300	288000	270000	250000	220000	150000	200000	250000	220000
2	SG	8900	8400	8200	7000	7600	7700	8200	230000	250000	240000	234000	197000	210000	230000	230000
3	KK	8700	9500	8700	9400	6800	8000	4300	250000	260000	240000	200000	150000	100000	80000	120000
4	R	10000	9870	8700	5400				340000	310000	320000	340000	320000	234000	250000	
5	SS	9680	8800	9800	9600	9400	8700	9100	424000	420000	370000	385000	328900	370900	348600	345000
6	SA	9700	9730	9400	9500	8400	8340	8900	348000	319000	310000	308200	320700	311000	298900	310000
7	R	8000	7600	6580	5400	6500	7200	6600	278000	237600	240000	253800	323000	328900	328100	330000
8	AK	5200	3500	2700	3200	3700	4500	5700	254000	214000	220000	226000	178000	98000	112000	198000
9	GS	9880	9770	9600	9480	9800	9570	9970	311000	298900	300000	310000	398000	320000	350000	380000
10	HK	9780	9200	8400	8400	7000	6700	7200	330000	310000	297000	289000	270000	198000	320000	330000
11	SK	9800	9700	9600	8500	8900	8540	8790	255000	220000	210000	210000	200000	220000	200000	250000
12	DG	6800	9800	7600	8900	9800	9200	9800	320000	320000	310000	340000	340000	320000	350000	357000
13	BA	9800	9200	9400	9700	8700	8400	8900	350000	330000	310000	340000	330000	320000	298900	330000
14	RK	9900	9700	9600	8500	8900	8540	7600	298600	287900	240000	268000	297000	280000	310000	330000
15	GS	9900	8300	8400	8600	8600	7600	8000	330000	320000	320000	330000	350000	369000	289000	270000
16	GK	8800	8700	8400	9000	8200	7700	6700	328000	323800	310000	298600	287900	268000	297000	157000
17	SK	10,000	9700	9340	9700	9100	8500	7000	238000	267000	280000	329800	310000	370000	340000	350000
18	PK	10000	9980	5400	4200	3200	3100	3000	328000	362800	340000	286900	284600	268000	176000	150000
19	WM	9200	8600	5700	4000	3800	3700	3500	324000	323000	320000	340000	350000	220000	200000	150000
20	AB	10,000	9800	9500	9700	8700	8500	6000	297000	280000	291000	310000	330000	350000	380000	346000
21	SS	9680	8750	9800	9540	9250	8590	9640	424000	420000	380000	385000	328900	370900	348600	345000
22	KS	10000	9980	10000	9900	8750	8800	8430	328000	362800	340000	286900	284600	268000	176000	150000
23	SK	11000	9875	8760					384000	367600	340000	362800	356000	298400		
24	AB	4500	5500	4300	3800	3200	3000	3000	328000	323800	310000	298600	287900	268000	297000	157000
25	KD	9900	9700	9600	8500	8900	8540	7600	310000	298000	310000	310000	278000	310000	330000	345000
26	K	9780	9500	8400	8600	7000	6700	6800	310000	298000	270000	279000	230000	198000	230000	324000
27	AB	9800	8790	9700	8700	8900	9000	8200	255000	220000	210000	210000	200000	180000	200000	200000
28	JK	5200	4800	3680		3700	4500	5700	254000	214000	230000	226000	178000	98000	112000	198000
29	SK	8900	8700	7200	6700	6820	7210	7200	210000	230000	210000	220000	198000	200000	220000	250000
30	AK	9800	9900	6800	5800	6700	7800	8900	279000	240000	250000	270000	323000	340000	340000	330000

S.no.	Name			B UREA												
		Fifth Month	Sixth Month	BASELINE	1st Week	2nd week	3rd Week	First Month	Second Month	Third Month	Fourth Month	Fifth Month	Sixth Month	BASELINE	1st Week	2nd week
1	AK	280000	210000	92	120	110	100	150	120	85	80	60	45	3.2	3	2.8
2	SG	279000	243000	96	90	88	76	62	56	45	34	30	32	3.2	3.4	3.4
3	KK	100000	110000	40	100	96	80	78	58	42	40	36	30	4	3.4	3.3
4	R			220	156	148	142	110	90	110				8.2	7.2	7
5	SS	356000	325800	75	58	50	45	38	36	28	36	33	28	2	1.8	1.6
6	SA	398000	320000	98	68	60	56	42	38	32	36	32	33	3.2	3	2.9
7	R	350000	380000	110	100	96	94	78	84	105	96	94	88	6	4.6	4.1
8	AK	217000	234000		110	96	84	74	60	68	74	76	72	7.4	8.4	7.7
9	GS	346000	380000	100	112	100	115	80	58	51	41	38	34	3.5	4.3	3.9
10	HK	340000	370000	110	82	86	76	60	45	37	34	36	30	3.2	3.1	2.8
11	SK	280000	230000	130	80	76	76	60	56	42	40	36	38	3.6	4.2	3.9
12	DG	33000	350000	98	100	94	90	85	52	40	41	40	43	3.5	4.3	4
13	BA	370000	330000	98	80	76	70	54		187	221	210		3.2	3	2.9
14	RK	323000	328900	100	93	90	82	77	52	43	34	36	38	5.2	4.5	4.5
15	GS	250000	240000	60	50	46	40	38	32	28	33	25	28	3.4	3	2.8
16	GK	210000	250000	100	84	80	73	64	72	64	76	86	80	5	5.2	5
17	SK	329000	340000	130	88	82	78	45	54	50	38	32	34	5.8	4.2	4.1
18	PK	170000	180000	110	120	110	96	90	83	88	100	84	94	5.6	6.4	7.4
19	WM	145000	130000	60	54	50	42	36	32	30	32	25	30	2.4	2	1.8
20	AB	327000	334000	120	141	132	130	100	82	77	52	58	46	6	5.7	4.5
21	SS	356000	325800	75	55	50	44	36	34	28	30	33	29	2.8	2.1	2
22	KS	176000	187000	120	110	121	148	112	83	88	100	84	94	8	6.4	7.2
23	SK			176	156	136	142	110	90					8.2	7.2	7
24	AB	112000	100000	137	124	118	95	98	84	86	90	96	88	5.6	5.2	4.8
25	KD	330000	340000	100	99	90	86	76	56	45	34	36	36	4.5	4	4.1
26	K	340000	368000	131	100	100	98	60	40	37	33	28	25	3.5	4.1	3.8
27	AB	198000	250000	110	92	87	74	58	45	38	32	36	38	3.6	4	3.9
28	JK	217000	234000	132	110	92	84	74	60	68	74	76	72	8.7	7	6.7
29	SK	276000	247000	96	90	92	88	85	66	48	38	32	30	3.2	3.4	3.2
30	AK	340000	326000	120	100	96	94	78	84	45	34	30	34	7	6.5	5.4

S.no.	Name	CREATININE							EGFR							
		3rd Week	First Month	Second Month	Third Month	Fourth Month	Fifth Month	Sixth Month	BASELINE	1st Week	2nd week	3rd Week	First Month	Second Month	Third Month	Fourth Month
1	AK	2.7	1.5	1.5	1	0.8	0.8	0.7	17	18	20	20	42	42	68	89
2	SG	3.1	2.7	1.8		1.3	1.3	1.3	16	15	15	17	20	33	48	48
3	KK	3.1	2	1.5	1	0.9	0.9	0.8	13	15	16	17	29	41	68	77
4	R	6.8	6.5	5.8	5.5				5	6	7	7	7	8	9	
5	SS	1.5	1.4	1.4	1	1	1	0.9	42	47	55	59	64	64	87	87
6	SA	2.8	2.4	1.4	1	1	1	0.9	22	24	25	26	31	60	90	90
7	R	3.8	3.4	2.8	2.7	2.5	3	3.2	8	11	12	13	15	19	20	22
8	AK	6.5	4.2	2.6	2.4	2.6	2.8	2.5	6	5	5	6	11	20	22	20
9	GS	3.8	2.2	1.6	1.2	1.3	1.3	0.8	20	15	17	18	35	51	60	65
10	HK	2.7	1.8	1.3	0.8	0.8	0.8	0.8	17	18	20	21	34	50	92	90
11	SK	3.5	3	2.2	0.9	0.8	0.8	0.8	15	13	14	16	19	28	81	94
12	DG	3.8	2.2	1.6	1.4	1	0.9	0.9	20	15	17	18	34	51	67	72
13	BA	2.8	2.4	1.4	1.2	1.2	1	1	22	24	25	26	31	60	72	72
14	RK	4.3	3.1	1.8	1	1	1	1	26	15	15	15	23	44	90	90
15	GS	2.2	1.5	1.2	1.2	1.3	1.1	0.8	21	24	26	35	56	73	73	66
16	GK	5	4.8	5	5.3	4.2	4.8	5.1	9	9	9	9	10	9	9	11
17	SK	3.7	3.1	3	1.2	1	0.9	0.8	8	12	12	14	17	18	53	76
18	PK	8.4	6.8	4.3	2.5	2.3	3.2	3.7	8	7	6	5	6	11	21	23
19	WM	1.7	1.5	1.2	1.2	1.3	1.2	0.7	32	40	45	49	57	74	74	67
20	AB	4	3.1	3	1.2	1	0.9	0.9	8	8	11	13	17	18	53	67
21	SS	1.8	1.5	1.4	1	0.9	0.9	0.9	25	36	38	43	54	58	87	99
22	KS	8.4	6.8	4.3	2.5	2.3	3.2	3.4	5	7	6	5	6	11	22	24
23	SK	6.8	6.5	5.8					6	7	7	7	7	9		
24	AB	5	4.8	4	3.7	3	2.7	3	8	9	10	9	10	12	13	17
25	KD	4.3	3.1	2.8	1.2	1	1	1	15	17	17	16	23	26	72	90
26	K	3.5	1.8	1.3	1.2	0.9	1	1	20	17	18	20	45	67	74	105
27	AB	3.8	3	2.2	1	0.9	0.9	0.8	15	13	14	14	19	27	71	81
28	JK	6.4	3.8	3.4	3	3.3	2.8	3.1	5	6	6	7	12	14	16	15
29	SK	3.1	1.6	1.3	1	0.9	0.8	0.8	16	15	16	17	38	49	67	76
30	AK	4.8	3.5	3	2.8	3	3.4	3.6	6	7	8	10	14	17	19	17

S.no.	Name			SODIUM												
		Fifth Month	Sixth Month	BASELINE	1st Week	2nd week	3rd Week	First Month	Second Month	Third Month	Fourth Month	Fifth Month	Sixth Month	BASELINE	1st Week	2nd week
1	AK	89	105	145	142	144	144	145	142	141	142	143	141	5.2	5	5
2	SG	48	48	137	141	140	138	134	137	136	134	134	136	4.5	4.7	4.5
3	KK	77	89	143	142	141	138	143	140	141	143	141	140	5.8	5.7	5.2
4	R			142	141	140	141	138	137	136				6.2	5.2	5
5	SS	96	99	138	136	137	137	136	137	139	141	140	141	5.5	5.4	4.7
6	SA	90	102	140	142	141	141	139	138	140	142	137	138	5	4.8	4.6
7	R	18	16	138	143	142	141	139	138	140	142	141	142	5.4	4.4	4.3
8	AK	18	20	138	136	136	141	143	137	140	142	140	137	5.4	4.4	4.4
9	GS	65	107	141	137	136	138	142	141	141	141	140	142	4.2	3.8	3.7
10	HK	90	90	137	138	40	134	136	135	137	138	140	139	4.9	4.2	4
11	SK	94	94	138	134	35	135	138	136	140	142	138	136	5.2	5.4	5.2
12	DG	76	76	141	140	142	137	141	142	139	142	140	143	4.2	3.8	4.1
13	BA	90	90	141	140	143	141	138	140	141	143	141	138	5	4.8	4.6
14	RK	90	90	141	140	136	136	132	138	134	136	138	136	3.7	3.8	4
15	GS	81	109	143	141	138	139	138	140	142	141	136	38	5.1	4.4	4.2
16	GK	10	9	138	137	141	137	136	141	137	138	141	143	4.8	4.2	3.8
17	SK	76	87	137	140	142	138	141	136	134	137	136	140		5.5	5
18	PK	15	13	138	136	137	138	141	141	139	137	140	141	5.7	4.8	4.7
19	WM	74	117	141	141	141	140	141	140	143	141	140	143	5.4	4.4	4.2
20	AB	76	76	140	141	141	141	140	136	132	138	136	40	5.4	5.2	5.2
21	SS	99	99	132	134	138	136	134	138	136	141	141	139	5.5	5.4	4.1
22	KS	16	15	134	136	135	138	143	141	139	138	140	142	5.7	4.8	3.3
23	SK			143	138	136	134	141	138					6.2	5.2	3.5
24	AB	20	17	135	137	135	132	136	141	137	138	141	143	4.8	4.2	4.3
25	KD	78	90	140	140	141	139	137	138	138	136	138	138	3.7	3.8	4
26	K	92	92	132	137	137	138	134	135	138	136	140	142	4.9	4.2	4.1
27	AB	81	94	136	134	141	135	137	141	140	142	138	136	5.5	5.4	4.7
28	JK	18	16	137	132	135	136	141	137	138	142	141	139	5.9	4.4	4.5
29	SK	88	88	134	136	137	138	134	127	132	134	132	134	4.5	4.7	4.6
30	AK	15	14	137	136	141	141	140	141	140	138	137	142	5.4	4.4	4.5

S.no.	Name	POTASSIUM							CRP							
		3rd Week	First Month	Second Month	Third Month	Fourth Month	Fifth Month	Sixth Month	BASELINE	1st Week	2nd week	3rd Week	4th week	Second Month	Third Month	Fourth Month
1	AK	5.2	4.8	4.6	4.2	4.1	4.5	4.3	48	30	28	22	7	5	5	4
2	SG	4.2	3.7	3.8	3.4	3.9	4	4	44	52	48	45	22	8	4	5
3	KK	5.4	4.8	4.5	4.2	4.3	4	3.8	44	30	23	18	5	4	5	7
4	R	4.7	4.6	4.4	4.5				100	100	95	94	82	80		
5	SS	4.4	4.8	4.6	3.9	4.2	4.5	5.1	29	18	15	10	8	6	4	3
6	SA	4.3	3.7	3.9	4.2	4.7	3.9	4.6	60	52	48	40	25	15	6	5
7	R	4.8	4.6	3.9	4.8	4.2	3.8	4.2	65	50	50	52	45	40	38	35
8	AK	4.8	4.2	3.8	3.4	3.2	4.2	4.1	100	86	82	78	68	50	36	26
9	GS	3.6	3.7	4.2	4.2	3.7	3.8	4.2	58	52	47	38	22	10	4	3
10	HK	3.9	3.4	3.6	4.2	4.1	3.8	3.8	58	28	16	12	8	2	2	3
11	SK	4.4	4.8	4.2	3.8	3.4	3.7	4.2	30	15	12	12	8	6	6	3
12	DG	3.8	3.7	4.2	4.2	3.7	3.8	4.2	58	52	45	38	22	10	4	3
13	BA	4.3	3.7	3.9	4.2	4.7	3.9	4.6	52	52	46	40	25	15	6	5
14	RK	3.6	3.9	4	4	3.8	3.5	3.6	54	43	37	32	6	5	3	4
15	GS	4.8	4.2	3.8	3.7	4.2	3.8	3.6	22	15	14	12	8	6	6	3
16	GK	3.8	4.4	4.8	4.2	4.8	4.6	3.9	48	22	25	30	24	20	14	7
17	SK	4.6	4.2	3.8	4	3.8	4	4.4	46	28	18	20	15	10	4	4
18	PK	4.6	5.4	4.4	4.8	4.6	3.9	4.9	80	68	64	60	56	44	35	28
19	WM	4.8	4.2	3.8	3.4	4.2	3.8	3.4	20	15	15	12	8	6	6	3
20	AB	4.6	4.2	3.8	4	3.8	4	4.4	52	28	24	20	10	6	4	4
21	SS	4.4	4.8	4.6	3.9	4.2	4.5	5.1	34	18	15	10	8	6	4	3
22	KS	4.6	5.4	4.4	4.8	4.6	3.9	4.9	88	68	63	60	56	44	35	28
23	SK	4.7	4.6	4.4					112	100	98	94	82	80		
24	AB	3.8	4.4	4.8	4.2	4.8	4.6	3.9	43	22	20	20	18	16	12	10
25	KD	3.7	3.9	4	4	3.8	3.5	3.6	54	44	40	32	15	7	3	4
26	K	3.9	3.4	3.6	4.2	4.1	3.8	3.8	45	28	22	12	8	2	2	3
27	AB	4.4	4.8	4.2	3.8	3.4	3.7	4.2	15	15	14	12	8	6	6	3
28	JK	4.8	4.2	3.8	3.4	3.2	4.2	4.1	100	86	79	78	68	50	36	26
29	SK	4.2	3.7	3.8	3.4	3.9	4	4	65	80	76	62	20	8	4	5
30	AK	4.8	4.6	3.9	4.8	4.2	3.8	4.2	60	40	36	35	28	20	16	12

S.no.	Name			ALBUMIN			TOTAL PROTEINS			URINE PROTEINS						
		Fifth Month	Sixth Month	baseline	3rd month	6th month	baseline	3rd month	6th month	BASELINE	1st Week	2nd week	3rd Week	First Month	Second Month	Third Month
1	AK	5	5	3.4	3.8	3.6	7.3	7.4	7	2+	2+	2+	1+	1+	0	0
2	SG	4	4	3.4	3.6	3.8	7.7	7.8	8	1+	1+	1+	1+	0	0	0
3	KK	5	5	3.5	4	4.2	7	7.4	7	2+	2+	2+	1+	1+	0	0
4	R			3.2	3.4		7.5	7.3		2+	2+	2+	2+	2+	2+	1+
5	SS	4	3	3.6	3.8	3.8	7.8	7.4	7.3	1+	1+	1+	1+	0	0	0
6	SA	5	2	3.5	3.8	4	7.2	7.5	7.6	3+	1+	1+	2+	1+	0	0
7	R	25	20	3.5	4.2	4.1	7.4	7.6	7.5	3+	2+	2+	2+	2+	1+	1+
8	AK	20	18	3.4	3.8	3.8	7	7.2	7	3+	2+	2+	2+	1+	1+	1+
9	GS	3	4	3.3	3.7	3.5	7.6	7.5	7.6	2+	1+	1+	1+	0	0	0
10	HK	3	4	3.1	3.6	3.7	7.3	7.1	7.2	2+	2+	2+	1+	1+	0	0
11	SK	5	4	3.4	3.6	3.8	7.6	7.9	8	1+	1+	1+	1+	1+	0	0
12	DG	3	4	3.3	3.7	3.5	7.6	7.5	7.6	2+	1+	1+	1+	0	0	0
13	BA	5	2	3.7	3.8	4	7.5	7.5	7.6	3+	1+	1+	2+	1+	0	0
14	RK	3	3	3.5	3.5	3.6	7.1	6.9	7	2+	1+	1+	1+	1+	1+	0
15	GS	5	4	3	3.6	3.8	7	7.3	7.2	2+	1+	1+	1+	0	0	0
16	GK	10	16	3.3	3.4	3.8	7.2	7.4	7.5	2+	2+	2+	2+	1+	1+	2+
17	SK	6	5	3.2	3.6	3.6	7.4	7.5	7.8	2+	2+	2+	2+	1+	0	0
18	PK	20	15	3.6	3.7	3.8	7.9	7.3	7.4	2+	2+	2+	2+	2+	2+	1+
19	WM	5	4	3.3	3.6	3.8	7.4	7.3	7.2	2+	1+	1+	1+	0	0	0
20	AB	6	5	3.2	3.6	3.6	7	7.5	7.8	3+	2+	2+	2+	1+	0	0
21	SS	4	3	3.2	3.8	3.8	7.2	7.4	7.3	1+	1+	1+	1+	0	0	0
22	KS	20	15	3.2	3.7	3.8	7.4	7.3	7.4	2+	1+	1+	2+	2+	1+	1+
23	SK			3.2			7.2			2+	2+	2+	2+	1+	1+	
24	AB	10	10	3.3	3.4	3.8	7.2	7.4	7.5	2+	2+	2+	2+	1+	1+	2+
25	KD	3	3	3.5	3.5	3.6	7.1	6.9	7	2+	1+	1+	1+	1+	1+	0
26	K	3	4	3.4	3.6	3.7	7.1	7.1	7.2	1+	1+	1+	1+	1+	0	0
27	AB	5	4	3.2	3.6	3.8	7.6	7.9	8	1+	1+	1+	1+	1+	0	0
28	JK	20	18	3.4	3.8	3.8	7	7.2	7	1+	2+	2+	1+	1+	1+	1+
29	SK	4	4	3.4	3.6	3.8	7.7	7.8	8	1+	1+	1+	1+	0	0	0
30	AK	10	15	3.6	4.2	4.1	7.7	7.6	7.5	3+	2+	2+	2+	2+	1+	1+

S.no.	Name				URINE RBCs											
		Fourth Month	Fifth Month	Sixth Month	BASELINE	1st Week	2nd week	3rd Week	4th week	Second Month	Third Month	Fourth Month	Fifth Month	Sixth Month	BASELINE	1st Week
1	AK	1+	1+	0	20	22	15	10	0	5	0	0	0	0	0	0
2	SG	0	0	0	15	12	10	8	0	6	0	0	0	0	6	0
3	KK	0	0	0	20	15	10	10	8	5	5	0	0	0	0	0
4	R				25	20	20	20	15	15	15				0	0
5	SS	0	0	0	10	10	8	5	5	0	0	0	0	0	0	0
6	SA	0	0	0	25	20	10	10	0	5	0	0	0	0	0	6
7	R	2+	1+	1+	25	18	15	14	8	4	2	0	0	0	0	5
8	AK	1+	2+	1+	22	18	15	15	12	15	15	10	10	8	6	0
9	GS	0	0	0	10	8	5	4	0	0	0	0	0	0	6	0
10	HK	0	0	0	15	8	10	5	0	0	0	0	0	0	2	0
11	SK	0	0	0	25	10	10	10	5	0	0	0	0	0	10	0
12	DG	0	0	0	10	6	10	4	0	0	0	0	0	0	8	2
13	BA	0	0	0	25	20	15	10	10	8	6	8	5	5	0	6
14	RK	0	0	0	25	10	10	10	6	4	0	0	0	0	0	0
15	GS	0	0	0	12	8	5	5	4	4	0	0	0	0	0	6
16	GK	1+	1+	1+	20	15	10	25	20	15	12	10	10	10	5	8
17	SK	0	0	0	20	15	10	10	10	0	4	0	0	0	0	0
18	PK	2+	1+	1+	20	20	15	15	15	12	10	10	15	10	0	0
19	WM	0	0	0	10	10	8	5	4	0	0	0	0	0	0	6
20	AB	1+	0	0	25	20	15		8	0	0	0	0	0	0	0
21	SS	0	0	0	10	10	10	10	5	3	0	0	0	0	0	0
22	KS	1+	1+	1+	20	20	20	15	15	15	18	15	15	10	0	0
23	SK				25	25	20	15	20	15					0	0
24	AB	1+	1+	1+	20	15	20	25	20	15	15	12	10	8	8	0
25	KD	0	0	0	20	10	10	10	6	0	0	0	0	0	0	0
26	K	0	0	0	25	10	5	4	0	0	0	0	0	0	4	0
27	AB	0	0	0	25	10	10	10	6	4	0	0	0	0	12	0
28	JK	1+	2+	2+	25	20	20	15	10	10	8	10	10	8	8	0
29	SK	0	0	0	15	12	10	8	8	6	0	0	0	0	8	0
30	AK	2+	1+	1+	25	20	15	15	18	15	15	15	12	10	0	5

S.no.	Name	URINE PUS CELLS								UPCR						
		2nd week	3rd Week	First Month	Second Month	Third Month	Fourth Month	Fifth Month	Sixth Month	BASELINE	1st Week	2nd week	3rd Week	First Month	Second Month	Third Month
1	AK	0	0	0	0	0	0	0	0	3.4	2.3	2	1.8	0.6	0.5	0.3
2	SG	0	0	0	0	0	0	0	0	2	2	1.8	1.5	1.2	1.3	1.5
3	KK	0	0	0	0	0	0	0	0	3	2.3	2	1.8	0.6	0.5	0.3
4	R		0	0	0	0				2.1	2	2	2	1.9	2	2.2
5	SS	0	0	6	0	0	0	0	0	1.4	1.8	1.5	1.3	1.4	1.5	1.2
6	SA	0	0	0	0	0	0	0	0	2	1.5	1.5	1.3	1.2	1	0.3
7	R	0	0	0	0	0	0	0	0	2.8	2.7	2.2	1.8	1.3	1.5	1.7
8	AK	0	0	0	8	0	0	0	0	2.1	2	2	1.9	1.8	1.4	1.5
9	GS	0	0	0	0	0	0	0	0	2.1	2.3	1.7	1.5	1	0.5	0.2
10	HK	0	0	4	0	0	0	0	0	2.8	2.1	1.8	1.4	0.9	0.3	0.1
11	SK	0	0	0	0	0	0	0	0	3.2	2.1	2	1.8	1.3	0.2	0.2
12	DG	0	0	0	0	0	0	0	0	2.3	1.9	1.8	1.5	1	0.5	0.2
13	BA	0	0	0	0	0	0	0	0	2.1	1.5	1.7	1.3	1.2	1	0.3
14	RK	0	0	0	0	0	6	0	0	2.8	2	1.8	1.6	1.3	0.9	0.7
15	GS	0	0	0	0	0	0	0	0	3.2	2.3	1.7	1.5	1.3	1.1	0.2
16	GK	0	0	0	0	0	0	0	0	1.7	2.8	2.6	2.4	2.1	1.8	2.2
17	SK	0	0	0	0	0	0	0	0	2.3	1.7	1.5	0.5	0.7	0.4	0.2
18	PK	0	0	0	0	0	0	0	0	2.8	2.5	2.4	2.2	2	1.7	1.5
19	WM	0	0	0	0	8	0	0	0	2.9	2.3	1.8	1.5	1.3	1.1	0.2
20	AB	0	0	0	0	0	0	0	0	2.7	1.7	1.3	0.5	0.7	0.4	0.2
21	SS	0	0	6	0	0	0	0	0	2	1.8	1.5	1.3	1.4	1.5	1.2
22	KS	0	0	0	0	0	0	0	0	2.8	2.5	2	2.2	2	1.7	1.5
23	SK	0	0	0	0					2.1	2	1.6	1.5	1.9	2	
24	AB	0	0	0	0	0	0	0	0	3.5	2.8	2.5	2.4	2.1	1.8	2.2
25	KD	0	0	0	0	0	6	0	0	2.4	2	2	1.6	1.3	0.9	0.7
26	K	0	0	4	0	0	0	0	0	3.4	2.1	1.5	1.4	0.9	0.3	0.1
27	AB	0	0	0	0	0	0	0	0	2.7	2.1	2	1.8	1.3	0.2	0.2
28	JK	0	0	0	8	0	0	0	0	2.5	2	2	1.9	1.8	1.8	1.7
29	SK	0	0	0	0	0	0	0	0	2	2	1.8	1.5	1.2	1.3	1.5
30	AK	0	0	0	0	0	0	0	0	1.8	2.7	2.5	1.8	1.3	1.5	1.7

S.no.	Name				BVAS										AN	
		Fourth Month	Fifth Month	Sixth Month	BASELINE	1st Week	2nd week	3rd Week	4th week	2nd month	Third Month	Fourth Month	Fifth Month	Sixth Month	TYPE	Baseline
1	AK	0.1	0.1	0.1	15	12	12	8	6	6	0	0	0	0	PR3	+
2	SG	1.3	0.1	0.2	15	10	10	8	6	0	0	0	0	0	MPO	+
3	KK	0.1	0.1	0.1	17	12	12	10	6	6	0	0	0	0	PR3	+
4	R				28	20	20	18	20	18	16				PR3	+
5	SS	1.1	0.1	0.1	16	12	12	10	6	4	0	0	0	0	PR3	+
6	SA	0.2	0.1	0.1	20	16	16	14	0	0	0	0	0	0	PR3	+
7	R	1.4	1.2	1.7	22	12	12	12	12	12	10	8	8	6	PR3	+
8	AK	1.3	1.3	1.1	22	20	20	18	15	12	8	6	6	6	PR3	+
9	GS	0.1	0.2	0.1	20	14	12	10	4	0	0	0	0	0	PR3	+
10	HK	0.4	0.2	0.2	20	16	16	12	8	8	0	0	0	0	PR3	+
11	SK	0.08	0.09	0.11	19	16	16	10	6	0	0	0	0	0	PR3	+
12	DG	0.1	0.2	0.1	20	14	14	10	6	4	0	0	0	0	PR3	+
13	BA	0.2	0.1	0.1	20	16	16	14	8	0	0	0	0	0	PR3	+
14	RK	0.4	0.1	0.08	15	12	12	10	8	6	0	0	0	0	PR3	+
15	GS	0.1	0.1	0.09	20	12	12	8	4	0	0	0	0	0	PR3	+
16	GK	1.8	2	1.5	21	20	20	18	14	14	12	8	8	8	PR3	+
17	SK	0.1	0.1	0.13	21	20	20	12	8	0	0	0	0	0	PR3	+
18	PK	1.3	1.2	1	25	22	22	20	20	16	16	16	10	10	MPO	+
19	WM	0.1	0.1	0.1	18	12	12	10	10	4	0	0	0	0	PR3	+
20	AB	0.1	0.1	0.12	20	20	20	12	6	0	0	0	0	0	PR3	+
21	SS	1.1	0.1	0.1	18	12	12	10	8	4	0	0	0	0	MPO	+
22	KS	1.3	1.2	1	25	22	22	20	20	16	16	16	10	10	MPO	+
23	SK				24	20	20	18	20	18					PR3	+
24	AB	1.8	2	1.5	24	20	20	18	12	8	8	6	8	8	PR3	+
25	KD	0.4	0.1	0.1	15	12	12	10	6	6	0	0	0	0	PR3	+
26	K	0.4	0.2	0.1	20	16	16	12	6	8	0	0	0	0	PR3	+
27	AB	0.08	0.09	0.1	20	16	16	10	8	0	0	0	0	0	PR3	+
28	JK	1.5	2	2.2	22	20	20	18	15	12	8	6	6	6	PR3	+
29	SK	1.3	0.1	0.2	18	14	14	8	6	0	0	0	0	0	PR3	+
30	AK	1.4	1.2	1.7	22	12	12	12	10	12	10	8	8	6	PR3	+

S.no.	Name	ICA			ANA	C3/C4	LIGHT MICROSCOPY						
		3rd Month	6th Month	CD19/20			TOTAL NO.OF GLOMERULI	NO.OF NORMAL GLOMERULI	NO.OF TOTALLY SCLEROSED GLOMERULI	NO.OF PARTIALLY SCLEROSED GLOMERULI	TOTAL CRESCENTS	CELLULAR CRESCENTS	FIBROCELLULAR CRESCENTS
1	AK	+	+	ND	NEG	NORMAL	18	2	4	4	8	6	2
2	SG	+	+	ND	NEG	NORMAL	16	4	3	0	9	5	3
3	KK	+	+	ND	NEG	NORMAL	18	2	4	4	8	6	2
4	R	+		ND	NEG	NORMAL	14	4	0	0	10	8	2
5	SS	+	+	ND	NEG	NORMAL	18	6	0	0	12	8	3
6	SA	NEG	NEG	ND	NEG	NORMAL	20	5	6	1	8	6	2
7	R	+	+	ND	NEG	NORMAL	18	2	5	1	10	4	2
8	AK	+	+	ND	NEG	NORMAL	22	2	1	1	18	8	6
9	GS	NEG	NEG	ND	NEG	NORMAL	15	2	3	1	9	8	1
10	HK	+	NEG	ND	NEG	NORMAL	22	0	4	2	16	12	4
11	SK	+	NEG	ND	NEG	NORMAL	19	1	3	0	15	10	3
12	DG	+	NEG	ND	NEG	NORMAL	15	2	3	1	9	8	1
13	BA	+	NEG	ND	NEG	NORMAL	20	5	6	1	8	6	2
14	RK	NEG	NEG	ND	NEG	NORMAL	18	4	0	0	12	10	1
15	GS	+	+	ND	NEG	NORMAL	10	2	2	1	5	2	1
16	GK	+	+	ND	NEG	NORMAL	20	5	3	2	10	3	3
17	SK	NEG	NEG	ND	NEG	NORMAL	10	0	2	1	7	6	1
18	PK	+	NEG	ND	NEG	NORMAL	20	0	2	1	17	10	3
19	WM	+	+	ND	NEG	NORMAL	10	2	2	1	5	2	1
20	AB	NEG	NEG	ND	NEG	NORMAL	10	0	2	1	7	6	1
21	SS	NEG	NEG	ND	NEG	NORMAL	18	6	0	0	12	8	3
22	KS	+	+	ND	NEG	NORMAL	20	0	2	1	17	10	3
23	SK			ND	NEG	NORMAL	14	4	0	0	10	8	2
24	AB	+	+	ND	NEG	NORMAL	20	5	3	2	10	3	3
25	KD	+	+	ND	NEG	NORMAL	18	4	0	0	12	10	1
26	K	NEG	NEG	ND	NEG	NORMAL	22	0	4	2	16	12	4
27	AB	+	+	ND	NEG	NORMAL	19	1	3	0	15	10	3
28	JK	+	+	ND	NEG	NORMAL	22	2	1	1	18	8	6
29	SK	+	NEG	ND	NEG	NORMAL	16	4	3	0	9	5	3
30	AK	+	+	ND	NEG	NORMAL	18	2	5	1	10	4	2

S.no.	Name					IMMUNOFLOURESCENCE					BV THICKENING	AAV	PLEX	HD	MP
		FIBROUS CRESCENTS	INTERSTITIAL INFILTRATES	INTERSTITIAL FIBROSIS	TUBULAR ATROPHY	IgG	IgM	IgA	C3	KAPPA / LAMBDA					
1	AK	0	MILD	N	N	NEG	NEG	NEG	NEG	NEG	Y	GPA	N	N	Y
2	SG	1	MILD	N	N	NEG	NEG	NEG	NEG	NEG	N	MPA	N	N	Y
3	KK	0	MILD	N	N	NEG	NEG	NEG	NEG	NEG	N	GPA	N	N	Y
4	R	0	SEVERE	Y	Y	NEG	NEG	NEG	NEG	NEG	Y	GPA	Y	Y	Y
5	SS	1	MILD	N	N	NEG	NEG	NEG	NEG	NEG	N	GPA	N	N	Y
6	SA	0	MILD	N	N	NEG	NEG	NEG	NEG	NEG	N	GPA	N	N	Y
7	R	4	MODERATE	N	N	NEG	NEG	NEG	NEG	NEG	Y	GPA	N	N	Y
8	AK	4	MODERATE	Y	Y	NEG	NEG	NEG	NEG	NEG	Y	GPA	N	N	Y
9	GS	0	MODERATE	N	N	NEG	NEG	NEG	NEG	NEG	Y	GPA	N	N	Y
10	HK	0	MILD	N	N	NEG	NEG	NEG	NEG	NEG	N	GPA	N	N	Y
11	SK	2	MILD	N	N	NEG	NEG	NEG	NEG	NEG	N	GPA	N	N	Y
12	DG	0	MILD	N	N	NEG	NEG	NEG	NEG	NEG	N	GPA	N	N	Y
13	BA	0	MODERATE	N	N	NEG	NEG	NEG	NEG	NEG	Y	GPA	N	N	Y
14	RK	1	MILD	N	N	NEG	NEG	NEG	NEG	NEG	N	MPA	N	N	Y
15	GS	2	MILD	N	N	NEG	NEG	NEG	NEG	NEG	Y	GPA	N	N	Y
16	GK	4	MODERATE	Y	Y	NEG	NEG	NEG	NEG	NEG	N	GPA	N	N	Y
17	SK	0	MILD	N	N	NEG	NEG	NEG	NEG	NEG	N	GPA	N	N	Y
18	PK	4	MODERATE	Y	Y	NEG	NEG	NEG	NEG	NEG	Y	GPA	N	N	Y
19	WM	2	MILD	N	N	NEG	NEG	NEG	NEG	NEG	N	GPA	N	N	Y
20	AB	0	MILD	N	N	NEG	NEG	NEG	NEG	NEG	Y	GPA	N	N	Y
21	SS	1	MODERATE	N	N	NEG	NEG	NEG	NEG	NEG	Y	GPA	N	N	Y
22	KS	4	MODERATE	Y	Y	NEG	NEG	NEG	NEG	NEG	N	MPA	N	N	Y
23	SK	0	SEVERE	Y	Y	NEG	NEG	NEG	NEG	NEG	Y	GPA	Y	Y	Y
24	AB	4	MODERTAE	N	N	NEG	NEG	NEG	NEG	NEG	N	GPA	N	N	Y
25	KD	1	MILD	N	N	NEG	NEG	NEG	NEG	NEG	N	MPA	N	N	Y
26	K	0	MILD	N	N	NEG	NEG	NEG	NEG	NEG	Y	GPA	N	N	Y
27	AB	2	MODERATE	N	N	NEG	NEG	NEG	NEG	NEG	N	GPA	N	N	Y
28	JK	4	MODERATE	Y	Y	NEG	NEG	NEG	NEG	NEG	N	GPA	Y	Y	Y
29	SK	1	MILD	N	N	NEG	NEG	NEG	NEG	NEG	N	GPA	N	N	Y
30	AK	4	MODERATE	N	N	NEG	NEG	NEG	NEG	NEG	N	GPA	Y	Y	Y

S.no.	Name	PREDNISOLONE DOSE			INDUCTION	REMISSION	OUTCOME	COMPLICATIONS
		BASELINE	3RD MONTH	6TH MONTH				
1	AK	60	12.5	5	RTX	Y	REMISSION	NONE
2	SG	60	12.5	5	CYC	Y	REMISSION	NONE
3	KK	60	12.5	5	CYC	Y	REMISSION	NONE
4	R	60			CYC	N	DEATH	SEPSIS
5	SS	60	12.5	5	CYC	Y	REMISSION	NONE
6	SA	60	12.5	5	RTX	Y	REMISSION	NONE
7	R	60	15	5	RTX	N	NO REMISSION	NONE
8	AK	60	15	5	CYC	N	NO REMISSION	NONE
9	GS	60	12.5	5	RTX	Y	REMISSION	NONE
10	HK	60	12.5	5	CYC	Y	REMISSION	NONE
11	SK	60	12.5	5	RTX	Y	REMISSION	NONE
12	DG	60	12.5	5	CYC	Y	REMISSION	NONE
13	BA	60	12.5	5	CYC	Y	REMISSION	NONE
14	RK	60	12.5	5	RTX	Y	REMISSION	NONE
15	GS	60	12.5	5	RTX	Y	REMISSION	NONE
16	GK	60	20	10	CYC	N	NO REMISSION	NONE
17	SK	60	12.5	5	CYC	Y	REMISSION	NONE
18	PK	60	20	10	CYC	N	NO REMISSION	PANCYTOPENIA
19	WM	60	12.5	5	CYC	Y	REMISSION	PANCYTOPENIA
20	AB	60	12.5	5	RTX	Y	REMISSION	NONE
21	SS	60	12.5	5	RTX	Y	REMISSION	INFUSION RELATED REACTIONS
22	KS	60	20	10	RTX	N	NO REMISSION	NONE
23	SK	60			RTX	N	DEATH	SEPSIS
24	AB	60	20	10	RTX	Y	PARTIAL REMISSION	PANCYTOPENIA
25	KD	60	12.5	5	CYC	Y	REMISSION	NONE
26	K	60	12.5	5	RTX	Y	REMISSION	NONE
27	AB	60	12.5	5	CYC	Y	REMISSION	NONE
28	JK	60	15	5	RTX	N	NO REMISSION	NONE
29	SK	60	12.5	5	RTX	Y	REMISSION	NONE
30	AK	60	15	5	CYC	N	NO REMISSION	NONE

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No. BFUHS/2K19p-TH/ 9227

Date 10/6/2019

The Principal,
DMC, Ludhiana.

Subject: Approval of Plan of Thesis.

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.05.2019 has approved the plan of thesis of **Dr. Sapna**, a student of your college for **DM Nephrology** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

A comparative study of rituximab and cyclophosphamide as induction therapy in ANCA associated vasculitis

Supervisor
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Note :

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16. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

A COMPARATIVE STUDY OF RITUXIMAB AND CYCLOPHOSPHAMIDE AS INDUCTION THERAPY IN ANCA ASSOCIATED VASCULITIS

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

Doctorate of Medicine

in

NEPHROLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

MARCH, 2019

DR SAPNA

Department of NEPHROLOGY

DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	A Compartive study of Rituximab and Cyclophosphamide as induction therapy in ANCA associated vasculitis
For the degree of	D.M Nephrology
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University	Baba Farid University of Health Sciences, Faridkot

Introduction: (ANCA)–associated vasculitis is a multisystem autoimmune syndrome characterized by vasculitis predominantly affecting small vessels and circulating autoantibodies to neutrophil cytoplasmic antigens. Renal involvement occurs in upto 70% of patients and is manifested as RPGN with pauci-immune necrotizing, crescentic glomerulonephritis.

Aim of Study: To assess the comparative efficacy of Rituximab versus conventional therapy (Cyclophosphamide) in ANCA associated vasculitis.

Materials & Methods: This prospective randomized controlled study will be conducted in Department of Nephrology at DMCH Ludhiana. All the patients presenting with features of ANCA associated vasculitis with renal involvement will be included in this study.

Clinical Significance: The partial efficacy and severe toxicity of current regimens indicate a need for better induction therapy in ANCA-associated vasculitis. There is an important unmet need for safer and more effective therapies in patients with ANCA associated vasculitis, especially those at highest risk for treatment toxicity and death, such as elderly patients and those with severe renal dysfunction.

Keywords: ANCA associated vasculitis, RPGN

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CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"A COMPARATIVE STUDY OF RITUXIMAB AND CYCLOPHOSPHAMIDE AS INDUCTION THERAPY IN ANCA ASSOCIATED VASCULITIS"** exist in the Department of Nephrology, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself under our supervision and guidance.

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5	TITLE OF THE TOPIC	A COMPARATIVE STUDY OF RITUXIMAB AND CYCLOPHOSPHAMIDE AS INDUCTION THERAPY IN ANCA ASSOCIATED VASCULITIS

6 BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Antineutrophil cytoplasm antibody (ANCA)-associated vasculitides are small-vessel vasculitides that include granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg–Strauss syndrome).[1]

ANCA-associated vasculitides affect small-to-medium-size blood vessels, with a predilection for the respiratory tract and kidneys.

The incidence is higher in men than in women. The overall annual incidence of vasculitis is 10-20/million with a peak between 65 and 74 years of age.[2]

Constitutional signs and symptoms, such as fever, myalgia, arthralgia, and malaise, often accompany small-vessel vasculitis. Cutaneous lesions, leukocytoclastic angiitis caused by vasculitis or granulomatous lesions, present as palpable purpura and nodules. Central nervous system disease usually results from involvement of the meningeal vessels. Gastrointestinal involvement has been reported in almost one half of the patients with AAV.[3]

The American College of Rheumatology (ACR) in 1990 had proposed classification criteria for seven vasculitis syndromes. This criteria was developed before wide spread ANCA testing, and PAN and MPA were not differentiated.[4]

The European Vasculitis Study Group (EUVAS) criteria for a diagnosis of AAV:

- History of a chronic inflammatory disease
- Exclusion of other causes (such as infection)

• Tissue biopsy showing characteristic histology on biopsy and/or positive ELISA for either PR3 or MPO antibodies with a classical ANCA on immunofluorescence.[4]

The majority of patients with these syndromes have ANCA detectable in the serum at the time of initial presentation.[5] Two types of ANCA are of clinical significance in patients with vasculitis. ANCA causing a cytoplasmic immunofluorescence pattern (C-ANCA) on ethanol-fixed neutrophils reacting with the neutrophil granule enzyme, proteinase 3 (PR3-ANCA) occur in over 80% of patients with GPA. In contrast, ANCA causing a perinuclear immunofluorescence pattern (P-ANCA) on ethanol-fixed neutrophils and reacting with myeloperoxidase (MPO-ANCA) occur in less than 10% of patients with GPA, but in the majority of patients with MPA.

Using enzyme linked immunoassay (ELISA), C-ANCA commonly has specificity for proteinase 3 (PR3-ANCA) and the most common P-ANCA commonly has specificity for Myeloperoxidase (MPO- ANCA). When used together, positive IFA with positive ELISA has a sensitivity of approximately 81% and a specificity of approximately 96% for pauci-immune crescentic GN.[6]

Renal involvement occurs in 70% of affected patients and is manifested as rapidly progressive glomerulonephritis with pauci-immune necrotizing, crescentic glomerulonephritis on biopsy.[7] Patients with ANCA associated glomerulonephritis usually present with hematuria, proteinuria, and serum creatinine

6.2 REVIEW OF LITERATURE

ANCA Associated Vasculitides (AAV) comprises a group of multi-systemic diseases affecting small-to-medium-sized vessels and is characterized by the presence of Anti-Neutrophil Cytoplasmic Antibodies (ANCA) with specificity for either Proteinase-3 (PR3) or Myeloperoxidase (MPO). Absence or paucity of immune complex deposits in vessel walls is very characteristic, hence the name "Pauci immune vasculitis".

In the 1970s, Fauci and Wolff [8] hypothesized that Wegener's granulomatosis was mediated by a hypersensitivity reaction and responded to the immunosuppressive effects of cytotoxic agents, including cyclophosphamide.

In the 1980s, two specific types of anti-neutrophil cytoplasmic antibodies (ANCA) were discovered to be associated closely with a restricted spectrum of vasculitis, including Wegener's granulomatosis[9]

The use of cyclophosphamide and glucocorticoids as induction therapy for AAV has improved the survival rates from 20 % to well over 80 % at 2 years[10]

Despite the improvement in outcomes, not all patients respond satisfactorily to CYC, and up to half of the patients who initially achieve remission relapse within the first 3–5 years.[11] Moreover, substantial toxicity associated with the long-term and repeated use of CYC and GCS has emerged as the principle challenge in the management of these patients. CYC is associated with leukopenia, severe infections, cancer, and ovarian failure.[12] The partial efficacy and severe toxicity of such regimens indicate a need for better induction therapy in ANCA-associated vasculitis

Rituximab is a B-cell–depleting anti-CD20 monoclonal antibody that has been approved by the European Medicines Agency and the U.S. Food and Drug Administration for the treatment of non-Hodgkin's lymphoma and rheumatoid arthritis.[13] Rituximab is a chimeric monoclonal antibody directed against the cell-surface protein CD20, a 297 amino acid phosphoprotein with four transmembrane domains, which is selectively expressed on the cells of B-lymphocyte lineage. The molecule thought to function as a calcium channel subunit and play a role in B lymphocyte activation, proliferation, and differentiation.[14] Binding of Rituximab to CD20 causes the death of the target cell by a variety of mechanisms including antibody-dependent cellular cytotoxicity via macrophages and natural killer cells, complement-mediated B cell lysis, apoptosis, and/or sensitization to cytotoxic agents or steroids.[15]

In ANCA-associated vasculitis, B-cell activation and levels of B-cell–activating factor correlate with disease activity.[16] CD20-positive, B-cell–rich, follicle-like areas containing autoreactive memory B cells with affinity for the ANCA antigen, proteinase 3, are present in Wegener's granulomas.[17] Cyclophosphamide suppresses the activation, proliferation, and differentiation of autoreactive B cells.[18] These findings of a pathogenic role of B cells and ANCAs in ANCA-associated vasculitis provide support for the use of a B-cell–targeted therapy. Sustained remissions have been reported in 80 to 90% of patients with refractory ANCA-associated vasculitis who were treated with rituximab.[19].Circulating B lymphocytes remain undetectable in the peripheral blood for about 6–12 months following treatment with Rituximab.[20]

The two randomized trials, RITUXVAS and RAVE, compared effectiveness of Rituximab compared with Cyclophosphamide as induction treatment in new onset AAV.

In RITUXVAS trial rituximab-based regimen was not superior to a conventional cyclophosphamide regimen when used as induction treatment in patients with ANCA-associated renal vasculitis, but it permits reduced exposure to CYC and the avoidance of maintenance immunosuppression.[21]

In RAVE trial, IV Rituximab was compared with oral cyclophosphamide. Rituximab and glucocorticoids is not inferior to the standard regimen in patients with severe AAV.[22]

These two trials had some differences. RITUXVAS ($n = 44$) included new patients with severe renal disease whereas RAVE ($n = 197$) included new as well as relapsing patients with well-preserved kidney function. Oral cyclophosphamide was used as a comparator in RAVE, whilst pulsed cyclophosphamide was used in RITUXVAS. In both trials, rituximab was administered as four infusions of 375 mg/m2 body surface area; however, in RITUXVAS, two or three cycles of cyclophosphamide were given in addition to rituximab. Prednisolone was tapered and stopped by 5 months in RAVE trial whilst it was reduced to 5 mg by 6 months and continued for the rest of the trial in RITUXVAS trial. Neither trial continued with maintenance immunosuppression in the rituximab group.

Both trials found similar efficacy between Rituximab and Cyclophosphamide based regimens for patients with new diagnosis of vasculitis. There were no differences in the time to remission for nephritis or pulmonary manifestations between the Rituximab and Cyclophosphamide groups

6.3 AIMS AND OBJECTIVES OF THE STUDY

1. To assess the comparative efficacy of rituximab versus cyclophosphamide in AAV

7.0 MATERIALS AND METHODS

This is an open-label, two-group, parallel design, randomized study of 30 patients of ANCA vasculitis comparing a Rituximab based regimen with IV Cyclophosphamide regimen in the treatment of active 'generalised' AAV. Patient will be divided into two treatment groups according to computer generated randomization list. Both groups will receive IV methylprednisolone, followed by IV Rituximab in one group and IV cyclophosphamide in second group.

Study visits will occur at baseline; at weeks 1, 2, 3, and 4; and monthly thereafter for 6 months. Disease activity will be measured on the basis of the BVAS. Written informed consent will be taken by all patients

7.1 SOURCE OF DATA

This study will be conducted in Department of Nephrology at DMCH Ludhiana from 1st march 2019.

All the patients presenting with features of ANCA associated vasculitis with renal involvement from will be included in this study

7.2 METHOD OF COLLECTION OF DATA

TREATMENT

Dose of Glucocorticoids

The initial dosage 1 mg/kg/day prednisone- equivalent, preceded by 1 to 3 boluses of methylprednisolone (7.5 to 15 mg/kg/day)

After the first 2–4 weeks of treatment, the dose of glucocorticoids will be reduced by approximately 10% every 1 to 2 weeks to achieve a half-dose (0.5 mg/kg/d) at approximately the third month of treatment

Dose of cyclophosphamide:

Intravenous "pulses" (boluses at regular intervals; 15 mg/kg, modified according to eGFR with a maximum of 1200 mg/pulse, every 14 days for 1 month then every 3 weeks)

Dose of rituximab

4 infusions of 375 mg/m2 each given at 1-week intervals.

INCLUSION CRITERIA

1. A new diagnosis of WG, MP or renal-limited vasculitis (RLV)
2. Renal involvement attributable to active WG, MP or RLV with at least one of the following:
   a) Biopsy demonstrating necrotizing glomerulonephritis.
   b) Red cell casts on urine microscopy or ≥ ++ haematuria
3. ANCA positivity ANCA positivity requires either (a) or (b)
   (a) PR3-ANCA by ELISA.
   (b) MPO-ANCA by ELISA.
4. Written informed consent

EXCLUSION CRITERIA

1. Previous cyclophosphamide, (greater than 2 weeks of an oral or IV pulse cyclophosphamide regimen).
2. Co-existence of another multisystem autoimmune disease, e.g. SLE, Henoch Schonlein Purpura, rheumatoid vasculitis, essential mixed cryoglobulinaemia.
3. Hepatitis B antigen positive or Hepatitis C antibody positive.
4. Pregnancy, breast feeding or inadequate contraception if female.

6. Live Vaccine within last 4 weeks.
7. Known HIV positive (HIV testing will not be a requirement for this trial).
8. Sepsis/ uncontrolled infections
9. Uncontrolled diabetes
10. Treatment Failures Caused by Uncontrolled Disease after 3 months of therapy will be excluded from study.

RANDOMISATION

Patients will be randomly assigned, in a 1:1 ratio, to investigational therapy (the rituximab group) or standard therapy (the control group), according to computer generated randomization list.

END POINTS

PRIMARY

1. Induction of complete/ partial remission by 6 months.
2. Treatment Failures Caused by Uncontrolled Disease(3 months)

SECONDARY

Efficacy

1. Response rate at 6 weeks (BVAS < 50% baseline)
2. Remission at 6 months (BVAS=0 for 2 months by 6 months)
3. Time to remission (BVAS=0)
5. Change in eGFR

Remission definition

Full clinical remission is indicated by complete absence of clinical disease activity using BVAS 2003: BVAS score 0 for 2 months. The absence of renal disease activity is indicated by stable or falling creatinine and the absence of red cell casts. Diagnosis of complete remission is supported by a normal C-

reactive protein. Sustained remission is defined by BVAS 0, maintained for at least 6 months.

Partial remission (PR) will be defined as clinically relevant improvement of disease activity without fulfilling the criteria for full clinical remission

Escape treatment

Failure to recover renal function:

In patients with renal-limited disease who remain dialysis-dependent, immunosuppressive therapy may be withdrawn after three months and patients will be considered treatment failure, may require switch over therapy. These patients will be withdrawn from study.

STUDY DESIGN

ENTRY

INCLUSION CRITERIA

⇩

RANDOMISATION (1:1)

⇩

RITUXIMAB	CYCLOPHOSPHAMIDE
375 mg/m^2 IV 4 doses	(3 – 6 months)
Methyl prednisolone 1g IV	Methyl prednisolone 1gIV
Prednisolone	Prednisolone

⇩

6 MONTHS

6 WEEKS : INITIAL ASSESSMENT

6 MONTHS : EFFICACY AND SAFETY

STATISTICAL ANALYSIS

Data will be described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups will be done using Student t-test and Mann Whitney *U* test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test will be performed and exact test will be used when the expected frequency is less than 5. A probability value (*p* value) less than 0.05 will be considered statistically significant. All statistical calculations will be done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

NO

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3 ?

ATTACHED HEREWITH

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PROFORMA

SR.NO:

PATIENT'S NAME: **FATHER'S NAME:**

AGE: **SEX:**

MRD NO: **PHONE NO.**

ADDRESS: **DOA/ DOD**

WEIGHT:

CHIEF COMPLAINTS:

Constitutional symptoms: Fever weight loss Fatigue/malaise

Joint: pain Swelling

Rash: ulcers Purpura

Urinary complaints: Hematuria Oliguria Dysuria

Edema:

Nasal discharge:

Chest pain:

Eyes : redness Discharge

Signature of candidate Signature of supervisor

PAST HISTORY: Diabetes Hypertension

FAMILY HISTORY: +/-

PERSONAL HISTORY

Smoking Alcohol Any other drug abuse

GENERAL PHYSICAL EXAMINATION

Blood pressure	Pulse	Respiratory Rate
SPO2	Temperature	JVP
Pallor	Icterus	Clubbing
Cyanosis	Edema	Lymphadenopathy
Rash		

Signature of candidate Signature of supervisor

SYSTEMIC EXAMINATION

CARDIOVASCULAR SYSTEM

RESPIRATORY SYSTEM

ABDOMEN

CEREBROVASCULAR SYSTEM

MASCULOSKELETAL SYSTEM

ENT EXAMINATION

EYE EXAMINATION

Signature of candidate

Signature of supervisor

INVESTIGATIONS	VALUE AT BASELINE (ENTRY)
Hb	
TLC	
DLC :N/L/M/E/B	
PLATELETS	
B. UREA	
S. CREATININE	
LFTSBilirubin T/D SGOT/SGPT/ALP TSP/SERUM ALBUMIN	
ANCA C3 /C4	
ANA / ANTI Ds DNA	
Anti GBM	
ANTI HCV/ HBV/HIV	
E GFR(CKD EPI)	
CRP	
RHEUMATOID FACTOR	
CHEST XRAY ULTRASOUND ABDOMEN Liver Kidney size Others	
URINE R/E Proteinuria RBCs others	
CD 19/20	
RENAL BIOPSY	

Signature of candidate

Signature of supervisor

TIME	1ST WEEK	3RD WEEK	1ST MONTH	2ND MONTH	3RD MONTH	4TH MONTH	5TH MONTH	6TH MONTH
Hb								
TLC								
DLCN/L/M/E/B								
PLT								
UREA								
CREATININE EGFR								
Na+								
K+								
Cl-								
CRP								
Urine Protein RBCs Casts other								
UPCR								
BVAS WG								
	3rd Month				6th Month			
ANCA								
CD 19/20								

Signature of candidate

Signature of supervisor

	Persistent	New/Worse	None
1. GENERAL			☐
a. arthralgia/arthritis	○	○	
b. fever (≥ 38 degrees C)	○	○	
2. CUTANEOUS			☐
a. purpura	○	○	
b. skin ulcer	○	○	
c. ***gangrene**	○	○	
3. MUCOUS MEMBRANES/EYES			☐
a. mouth ulcers	○	○	
b. conjunctivitis/episcleritis	○	○	
c. retro-orbital mass/proptosis	○	○	
d. uveitis	○	○	
e. ***scleritis**	○	○	
f. ***retinal exudates/haemorrhage**	○	○	
4. EAR, NOSE & THROAT			☐
a. bloody nasal discharge / nasal crusting / ulcer	○	○	
b. sinus involvement	○	○	
c. swollen salivary gland	○	○	
d. subglottic inflammation	○	○	
e. conductive deafness	○	○	
f. ***sensorineural deafness**	○	○	
5. CARDIOVASCULAR			☐
a. pericarditis	○	○	
6. GASTROINTESTINAL			☐
a. ***mesenteric ischemia**	○	○	
7. PULMONARY			☐
a. pleurisy	○	○	
b. nodules or cavities	○	○	
c. other infiltrate secondary to WG	○	○	
d. endobronchial involvement	○	○	
e. ***alveolar hemorrhage**	○	○	
f. ***respiratory failure**	○	○	

	Persistent	New/Worse	None
8. RENAL			☐
a. hematuria (no RBC casts) (≥ 1 + or ≥ 10 RBC/hpf)	○	○	
b. ***RBC casts**	○	○	
c. ***rise in creatinine > 30% or fall in creatinine clearance > 25%**	○	○	
Note: If both hematuria and RBC casts are present, score only the RBC casts (the major item).			
9. NERVOUS SYSTEM			☐
a. ***meningitis**	○	○	
b. ***cord lesion**	○	○	
c. ***stroke**	○	○	
d. ***cranial nerve palsy**	○	○	
e. ***sensory peripheral neuropathy**	○	○	
f. ***motor mononeuritis multiplex**	○	○	
10. OTHER (describe all items and * items deemed major)			☐
Major			
☐ _____	○	○	
☐ _____	○	○	
☐ _____	○	○	
☐ _____	○	○	

11. TOTAL NUMBER OF ITEMS: ☐

a.	b.	c.	d.
___ ___	___ ___	___ ___	___ ___
Major New / Worse	Minor New / Worse	Major Persistent	Minor Persistent

DETERMINING DISEASE STATUS:
Severe Disease / Flare: ≥ 1 new/worse Major item
Limited Disease / Flare: ≥ 1 new/worse Minor item
Persistent Disease: Continued (but not new/worse) activity
Remission: No active disease, including either new /worse or persistent items

12. CURRENT DISEASE STATUS (check only one)

- Severe Disease/Flare ☐
- Limited Disease/Flare ☐
- Persistent Disease ☐
- Remission ☐

13. PHYSICIAN'S GLOBAL ASSESSMENT (PGA)
Mark to indicate the amount of WG disease activity (not including longstanding damage) within the previous 28 days:

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

Remission **Maximum activity**

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....

.....am willing to participate in the study **"A COMPARATIVE STUDY OF RITUXIMAB AND CYCLOPHOSPHAMIDE AS INDUCTION THERAPY IN ANCA ASSOCIATED VASCULITIS"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

.....
Signature of the Witness

Name:

.....
Signature of the patient

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"A COMPARATIVE STUDY OF RITUXIMAB AND CYCLOPHOSPHAMIDE AS INDUCTION THERAPY IN ANCA ASSOCIATED VASCULITIS"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____
गवाह के हस्ताक्षर
नाम:

_____
रोगी के हस्ताक्षर/अंगूठे का निशान
नाम:

_____
अन्वेषक के हस्ताक्षर

_____
विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"A COMPARATIVE STUDY OF RITUXIMAB AND CYCLOPHOSPHAMIDE AS INDUCTION THERAPY IN ANCA ASSOCIATED VASCULITIS" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ